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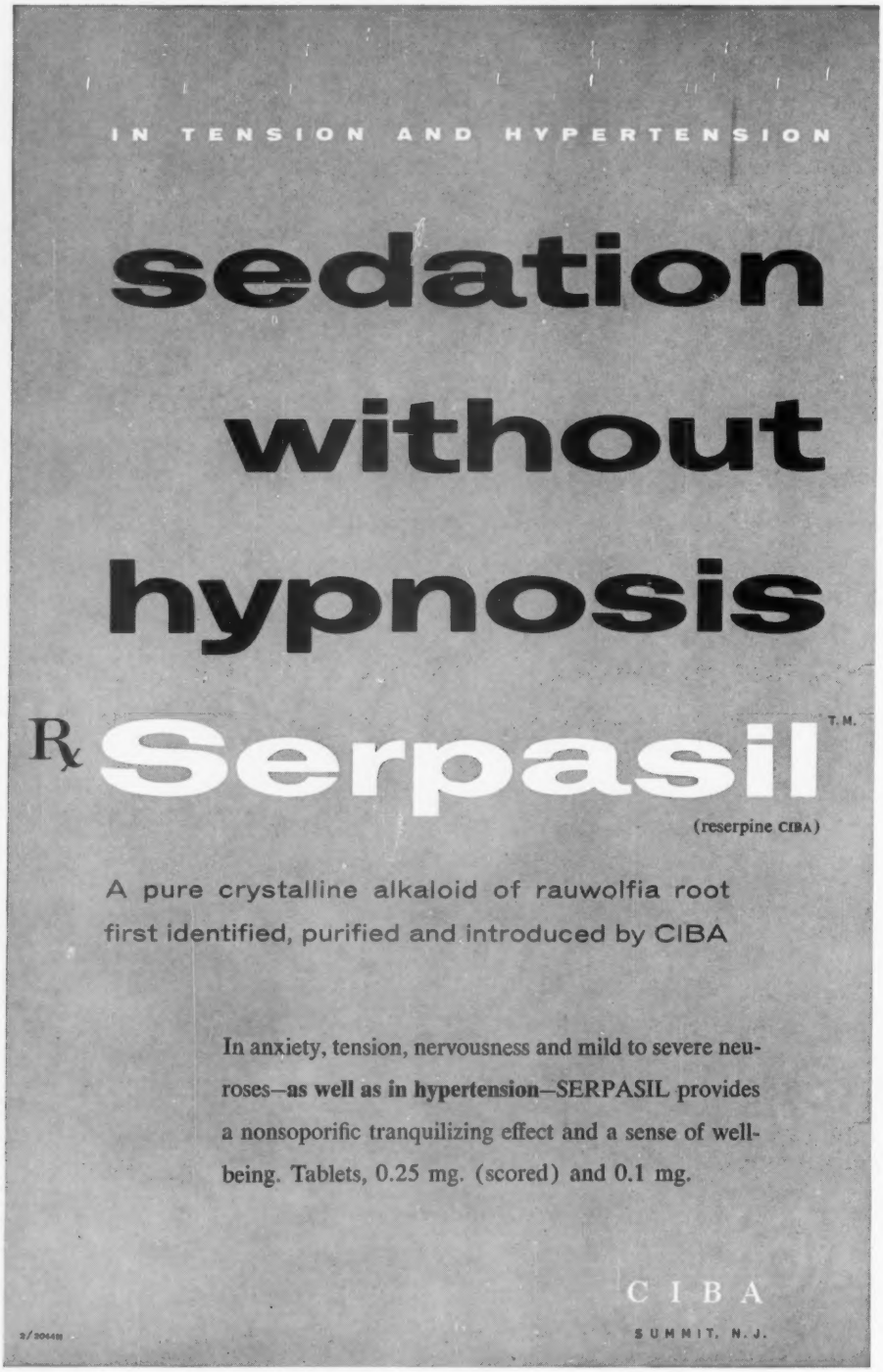
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1. Rechtman, A. M., and Yarrow, M. W.: Osteoporosis, Am. Pract. & Digest Treat. 5:691 (Sept.) 1954.
2. Cannon, P. R.; Frazier, L. E., and Hughes, R. H.: Factors Influencing Amino Acid Utilization in Tissue Protein Synthesis, in Symposium on Protein Metabolism, New York, The National Vitamin Foundation, Inc., 1954, pp. 55-90.

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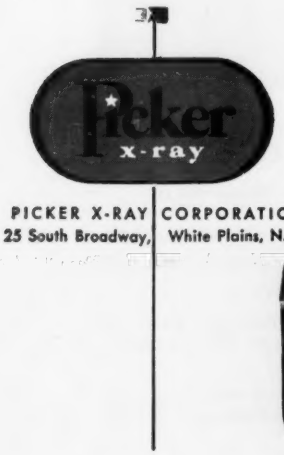

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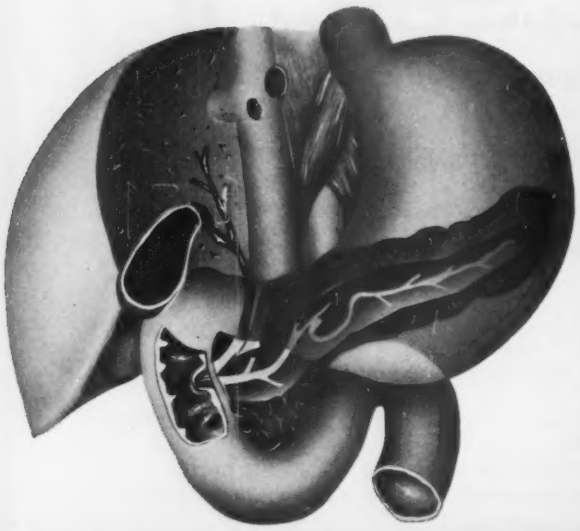

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*King, J. C.: Am. J. Digest. Dis. 22:102, April, 1955.

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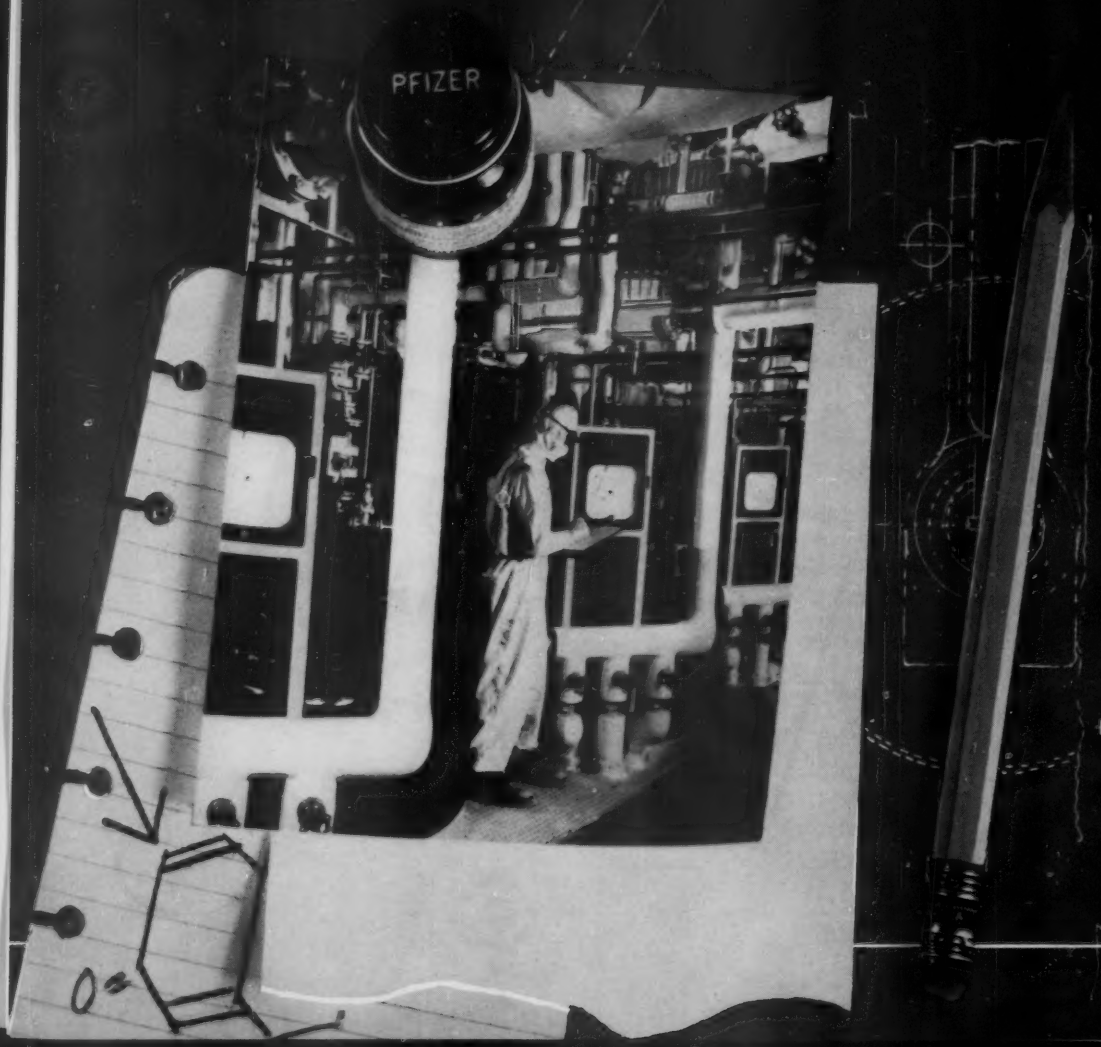

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1. Bunim, J. J., et al.: J.A.M.A. 157:311, 1955. 2. Boland, E. W.: California Med. 82:65, 1955. 3. Norred, S. R.: Am. Prof. Pharm. 21:241, 1955. 4. Waine, H.: Bull. Rheumat. Dis. 5:81, 1955. 5. Herzog, H. L., et al.: Science 121:176, 1955. 6. Spies, T. D.: GP, in press.

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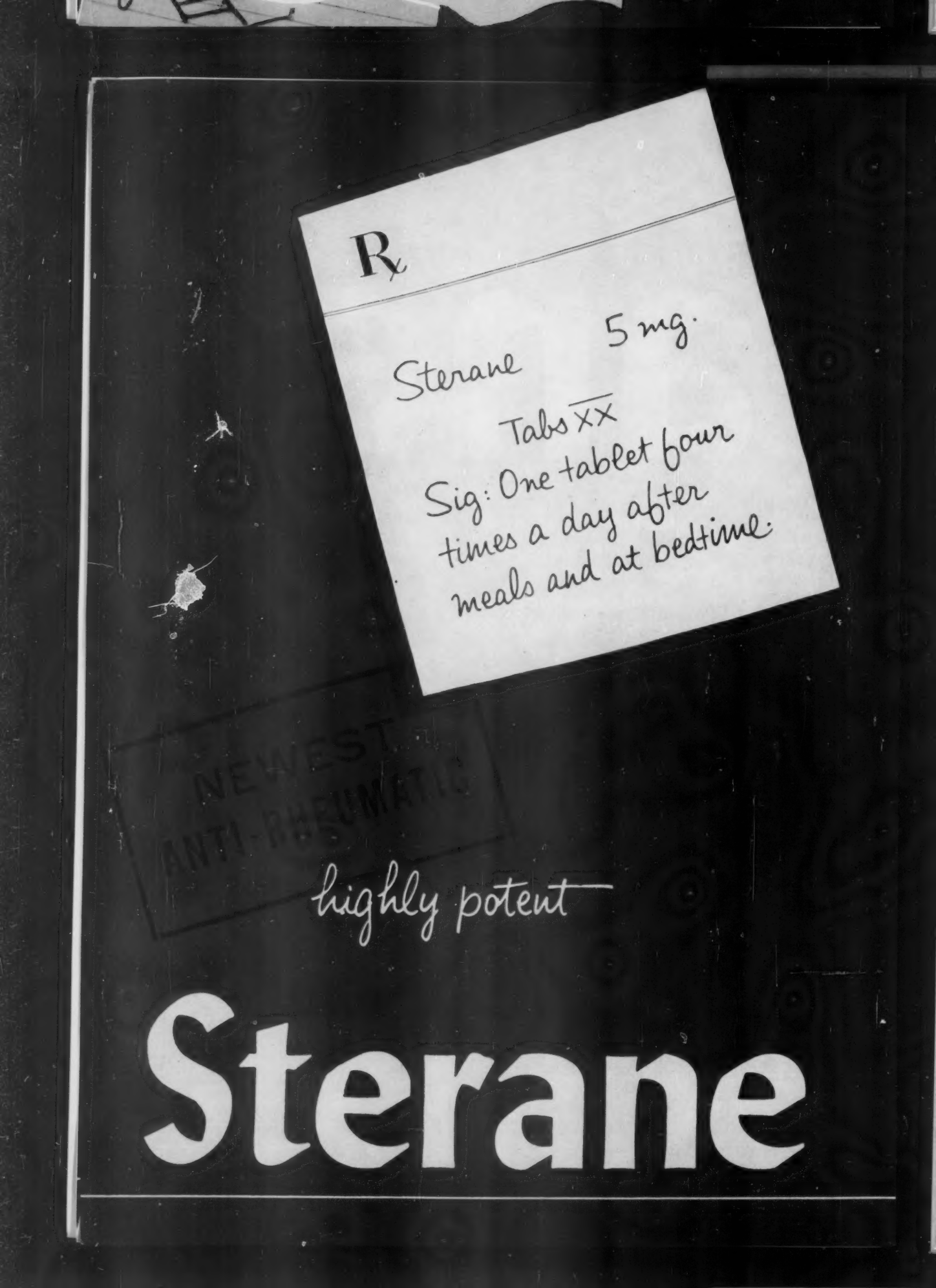
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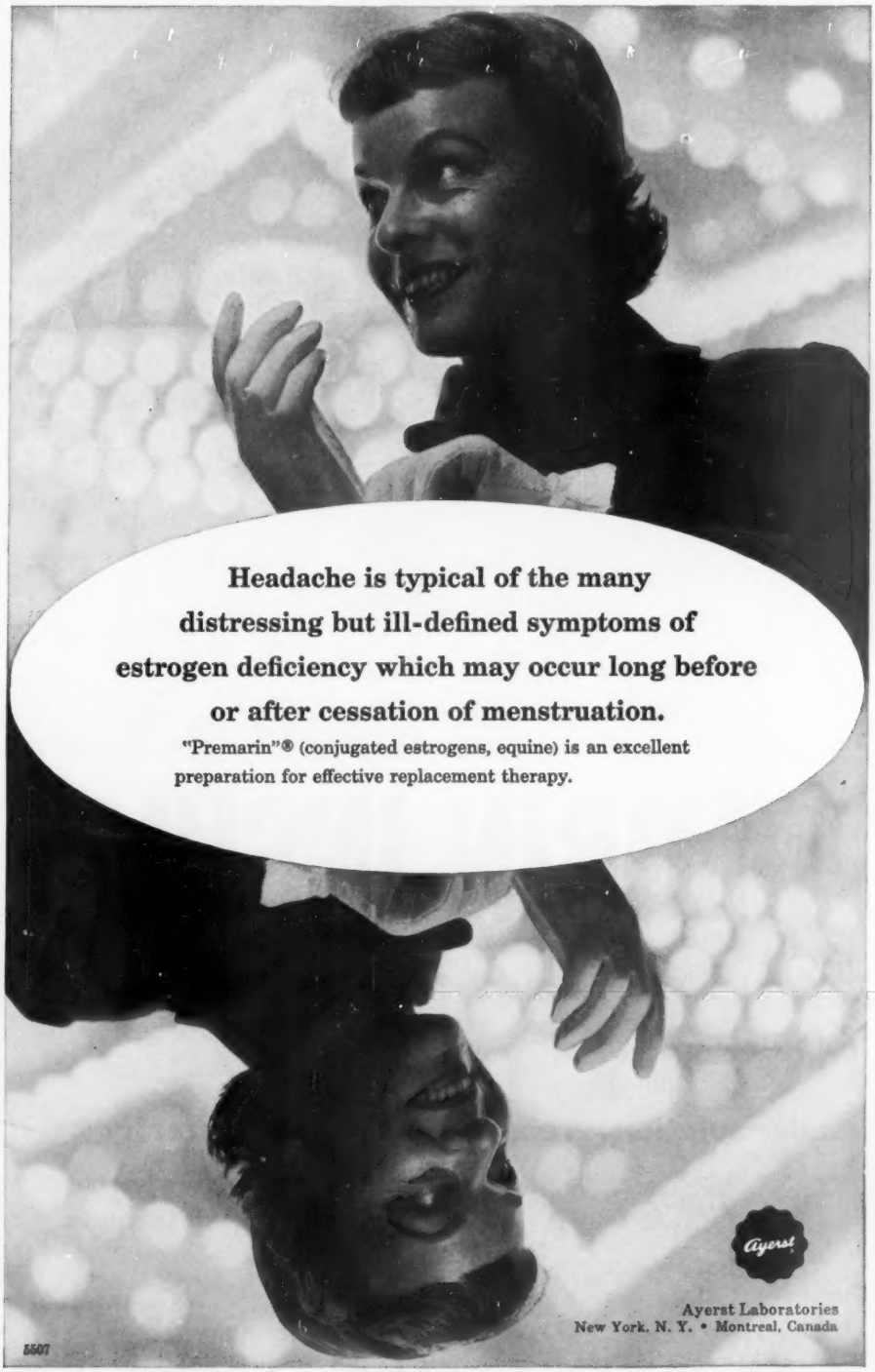
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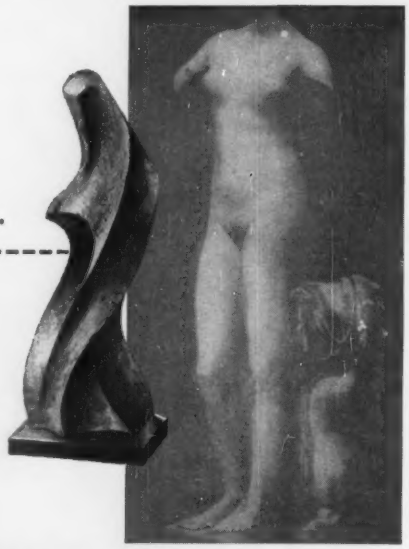

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Volume 253 JULY 14, 1955 Number 2

OCCURRENCE OF THYROID CANCER IN SAN FRANCISCO*

MERRILL J. ALEXANDER, M.D.†

SAN FRANCISCO

IN the literature, the occurrence of cancer of the thyroid gland has been studied at numerous teaching hospitals and large clinics by comparison, over a period, with the type of goiter seen clinically, with the number of thyroid operations, with the number of deaths or with the number of autopsies. Sokal,[1] after estimating prevalence and incidence by combining clinical data, mortality statistics and autopsy statistics, presents his conclusions in a more tangible and vivid manner. He states that in a hypothetical city of 1,000,000 there would be 25 patients with thyroid cancer at any given time, that on the average 1 new case would appear each month, and that there would be 6 deaths per year from this cause, 1 or 2 of which would be studied at autopsy.

METHOD

The occurrence of cancer of the thyroid gland has been studied in San Francisco, a community of 800,000, in the four-year period 1950-53, inclusive. The hypothesis applied would allow 20 cases at any given time, with 10 new cases diagnosed each year and 5 deaths each year.

Every hospital in San Francisco was visited, and every case of thyroid cancer listed in the disease index of the medical-record room, the surgical pathology laboratory and the tumor-board registry of each hospital was screened for permanent address in San Francisco at the time of the initial diagnosis within the years 1950-1953, inclusive. These cases were then evaluated for age, pathological type of cancer, clinical structure of the gland, presence of metastases and type of surgical treatment. No presumptive cases were included but only those positively diagnosed by tissue sections. In some cases the data available were sufficient for inclusion as bona-fide cases but insufficient for the complete evaluation. Disparity of numbers and totals of numbers are noted for this reason.

*The second-prize-winning essay of the San Francisco Surgical Society Essay Contest, 1953-54.

From the General Surgical Service, Veterans Administration Hospital.

†Resident, General Surgical Service, Veterans Administration Hospital.

RESULTS

San Francisco is the medical center for Northern California and some neighboring states. It was found that over two thirds of the cases in its hospitals were in patients living outside the city limits (Fig. 1). The 105 new cases, an average of 26 per year, in residents of San Francisco concerned socially normal members of the community, working regularly, attending

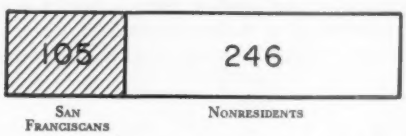

FIGURE 1. *Distribution of Cases Found in San Francisco Hospitals.*

school or keeping house. It is believed that they do not reflect a selected group in any way. Especially noteworthy is the fact that these patients were treated in all the hospitals, seen by a variety of examiners and operated on by various surgeons, and the tissues diagnosed by different pathologists. Numerous tumor boards reviewed the cases and recommended treatment. Consequently, these cases reflect the acumen of the composite medical profession in practice daily in a large metropolitan area and do not represent special selection as might necessarily be present in studies from a large teaching hospital or medical center.

All hospitals where surgery is done were included in the study and these included 12 private, 1 industrial, 2 teaching and 2 governmental hospitals (Fig. 2).

During each of the four years the occurrence of cancer of the thyroid gland (much greater than the hypothetical occurrence) increased steadily, possibly indicating increasing awareness and greater dispatch in the surgical management of the nodular goiter (Fig. 3). Indeed, removal of a thyroid nodule found on routine physical examination often demonstrated carcinoma. In the same figure the cases with metastases‡ at the time of initial diagnosis are indicated by

‡Includes invasion by direct extension, as well as by lymphatic or hematogenous spread.

TABLE 1. *Comparative Statistics in Various Reports on Cancer of the Thyroid Gland.*

SOURCE OF DATA	CLINIC	CITY	PERIOD	NO. OF CASES	CLASSIFICATION OF CASES	FREQUENCY IN ALL CASES	FREQUENCY IN ALL SOLITARY NODULES	FREQUENCY IN NON-TOXIC SOLITARY NODULES	FREQUENCY IN TOXIC SOLITARY NODULES
						%	%	%	%
Beahrs et al.[2]	Mayo	Rochester, Minn.	1938-1947	3,121					
Brenizer & McKnight[3]				2,324					
Cattell & Colcock[4]	Lahey	Boston, Mass.	1951-1952	78	Thyroid operation	5.3		33.3	
Cole et al.[5]	Univ. of Ill.	Chicago, Ill.	1936-1944	522	Thyroid surgery Nodular goiter			24.0	
Cole et al.[5]	Univ. of Ill.	Chicago, Ill.	1944-1948	141	Nodular goiter			25.5	
Cole et al.[5]	Univ. of Ill.	Chicago, Ill.	1936-1948	663	Nodular goiter			24.4	
Cole et al.[5]	Univ. of Ill.	Chicago, Ill.	1936-1948	378	Diffuse toxic goiter				
Cope et al.[6]	Harvard (Mass. Gen.)	Boston, Mass.	1937-1948	130	All surgical goiters		19.0		
Crabtree & Hunter[7]	Univ. of Mich.	Ann Arbor, Mich.	1935-1950	1,928	All thyroidectomies, nodularity determined in pathological specimen	7.21	24.30		
Crile & Hazard[8,9]	Crile	Cleveland, Ohio	1948				24.5		
Dailey et al.[10]	Univ. of Cal.	San Francisco, Cal.		3,539	Thyroidectomy		13.5		
Dailey et al.[10]	Univ. of Cal.	San Francisco, Cal.			Patients under 20 yr.				
Foss[11]	Geissinger Municipal	Danville, Pa.			Average of 11 authors	2.37			
Frantz et al.[12]	Columbia Univ.	New York City	1924-1944	4,707	Thyroidectomies				
Hendrick & Reed[13]							17.8		
Hinton & Lord[14]		New York City		184	Clinically benign nodular goiter				
Horn & Ravdin[15]	Univ. of Pa.	Phila., Pa.	1945-1950	22	Surgical goiters in patients under 25 yr.	3.0			
Horn et al.[16]	Univ. of Pa.	Phila., Pa.	1933-1945	2,079	Thyroidectomy (all diseases)	3.0			
Horn et al.[16]	Univ. of Pa.	Phila., Pa.		1,135	Thyroidectomy for nodular goiter				
Kennedy[17]	Mayo	Rochester, Minn.		62	Patients under 14 yr.				
Lahey & Hare[18]	Lahey	Boston, Mass.		1,971 1,782	All solitary adenomas Multiadenomatous goiters		10.0		
Lange & Maclean[19]	Univ. of Mich.	Ann Arbor, Mich.	1935-1945	1,326	All surgical goiters	4.6			
Pemberton & Black[20]	Mayo	Rochester, Minn.	1907-1947	3,500					
Pemberton & Black[20]	Mayo	Rochester, Minn.			Children				
Pemberton & Lovelace[21]								10.0	
Sokal[1]	Yale	New Haven, Conn.						20.0	
Stubenbord & Noehren[22]	Deaconess Hospital	Buffalo, N. Y.	(20 yr.)	2,106		2.08	3.08	3.86	1.72
Ward[23]	Univ. of Cal.	San Francisco, Cal.		3,539					
Ward[23]	Univ. of Cal.	San Francisco, Cal.		5,439		3.0	15.6		
Ward[23]	Univ. of Cal.	San Francisco, Cal.		10	Patients under 14 yr.				
Warren et al.[24]	Harvard	Boston, Mass.		23,000	Thyroid operation	2.5			
Warren et al.[24]	Harvard	Boston, Mass.			Patients under 20 yr.	3.7			

TABLE 1 *(Concluded).*

SOURCE OF DATA	FREQUENCY IN ALL MULTINODULAR GOITERS	FREQUENCY IN NONTOXIC MULTINODULAR GOITERS	FREQUENCY IN TOXIC MULTINODULAR GOITERS	FREQUENCY IN ALL NONTOXIC GOITERS	FREQUENCY IN ALL NONTOXIC NODULAR GOITERS	FREQUENCY IN ALL TOXIC NODULAR GOITERS	FREQUENCY IN TOTAL NODULAR GOITERS	FREQUENCY IN TOXIC DIFFUSE GOITERS	FREQUENCY IN ALL DIFFUSE GOITERS	FREQUENCY IN THYROTOXICOSIS
	%	%	%	%	%	%	%	%	%	%
Beahrs et al.[2]				3.8	7.5	1.2	4.8	0.5		
Brenizer & McKnight[3]							4			
Cattell & Colcock[4]					10.2	1.8	9.1			
Cole et al.[5]		11.0	1.6		17.1	1.2	7.2			
Cole et al.[5]		7.1			17.2		11.3			
Cole et al.[5]		9.8			17.15		8.0			
Cole et al.[5]								0.2		13.2
Cope et al.[6]							10.1	0.8		
Crabtree & Hunter[7]	7.54						9.0		0.63	25.0
Crile & Hazard[8,9]							5.6			
Dailey et al.[10]				4.8						
Dailey et al.[10]					59.0					
Foss[11]										
Frantz et al.[12]				6.8						
Hendrick & Reed[12]										
Hinton & Lord[14]							7.6			
Horn & Ravdin[15]				30.6			6.3			
Horn et al.[16]										
Horn et al.[16]				5.5			5.5			
Kennedy[17]							19.3			
Lahey & Hare[18]	0.62									
Lange & Maclean[19]							6.94			
Pemberton & Black[20]							4.8	0.4		
Pemberton & Black[20]							34			
Pemberton & Lovelace[21]										33.5
Sokal[1]										
Stubenbord & Noehren[22]	2.82	4.68	0.32		7.0		3.0			
Ward[23]							4.8			
Ward[23]										
Ward[23]					40.0					
Warren et al.[24]										
Warren et al.[24]										

toxic, and various combinations. All the statistics from the many studies have been assembled for quick comparison and ready comprehension in Table 1. It should be noted that the different series vary in the types of cases studied and that some are limited to children. All figures represent the percentage of cases that were malignant.

Factors in Incidence Studies

Incidence figures must be carefully studied before one can apply them at large. Cole et al.[5] note that many patients with goiters are not operated on and that the frequency of cancer in patients undergoing thyroidectomy therefore differs from that in patients at large with goiter. The incidence in cases of goiter should be considered as occurring in patients referred to the surgeon or charity hospital. Cope and his associates[6] also emphasize the fact that these series are in hospital-selected cases. Goiter is a geographic disease, and Cole, Majarakis and Slaughter[5] suggest that the cancer itself, as well as the invasive character of carcinomas in the thyroid gland, may have a geographic factor. In unselected nodular goiters Sokal[1] believes that fewer than 1 per cent are malignant.

Age is a significant factor in the occurrence of the type of the cancer and the prognosis.[8] The danger of a malignant lesion in a nodule in a male is three times greater than that in a female.[5]

Clinical Factors

Several clinical conclusions are noteworthy from the studies already published. In physical examination routine palpation of the thyroid gland has revealed unknown nodules that on removal have proved to be carcinoma. Cattell and Colcock[4] found this to be true in 9 out of 78 cases of carcinoma. Yet nodules are also overlooked at clinical examination and are frequently described where none exist.[19] In 100 autopsies it was found that 59 patients had diffuse nodular goiters, only 7 of which were detected by external examination.[19] Twenty-two adenomas were found only on pathological examination, even though some were 1.9 cm. in diameter. Cope et al.[6] call attention to the value of palpating for the Delphian lymph node (may be multiple) in the midline superficial to the cricoid cartilage, which may be involved by metastasis from carcinoma in any site in the thyroid gland. In 13 cases of thyroid carcinoma the Delphian lymph node was positive in 9 cases and palpable in 5.

Since the clinical diagnosis of thyroid cancer is difficult to make and since the disease is unrecognized clinically sufficiently often in nodular goiter, removal of all discrete nodules and thyroidectomy are warranted for goiters showing appreciable increase in size.[2,4] Kennedy, as cited by Cope and his associates,[6] indicates that children with any mass in the thyroid gland should be suspected of having a malignant process.

Treatment Factors

Cole has followed the policy in his department in recent years of advising every patient with a solitary thyroid nodule to have it removed. Warren and his co-workers believe that any nodule should be removed to prevent the development of a thyroid carcinoma, and Jackson[25] concurs, stating, "Cancer of the thyroid is the most easily preventable type of malignant growth since it arises in a pre-existing adenoma in 9 out of 10 cases and further that it would therefore be eliminated in 90 per cent of cases if all adenomas were removed when found." More radical approach to the treatment of thyroid carcinoma is urged by Frazell and Foote.[26]

Cope et al.[6] hesitate to recommend prophylactic surgery for any nodular goiter but consider it the sensible management for the solitary nodular goiter. The ratio of occurrence of cancer in multinodular and solitary nodular glands (Fig. 5) does not support them on this point in this community.

At Cleveland Crile[9] advises removal of all solitary nodules in youth, of all discrete, firm, solitary nodules in middle-aged persons and only nodules firm in consistence and those with a history of recent growth occurring in patients over sixty.

Prognostic Factors

Prognosis depends on the type of carcinoma, the age of the patient, the extent of disease at the time of initial treatment, the extent of surgery and radiosensitivity. Nine of 78 patients described by Cattell and Colcock[4] were dead from the carcinoma less than two years after operation. Crile[9] considers carcinoma to be of low malignancy in patients under forty years. With metastases and invasion as criteria for malignancy it appears that the lesions in patients under forty are as malignant as those in patients over forty in this study.

Summary

The actual incidence of diagnosed cancer of the thyroid gland in a community of 800,000 was 26 per year as compared to the hypothetical value of 10 per year. The demonstrated prevalence rate was far in excess (by at least 400 per cent) of the hypothetical value of 20.

Deaths per year exceeded the hypothetical value by at least 40 per cent.

The literature is reviewed, and frequency studies of cancer of the thyroid gland are compared.

Factors in the incidence, clinical evaluation, treatment and prognosis of thyroid cancer are presented from a review of the literature.

Since preparation of this paper 3 more cases falling within the requisites of this study have occurred. In addition Sokal[27] has presented another study, which suggests a significantly higher incidence of thyroid cancer, — namely, 2.2 per 100,000 population per year, as compared with a previously reported rate of 1.3 per 100,000 population per year. The actual incidence for San Francisco in this study is 3.4 per 100,000 per year.

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OCCURRENCE OF PAINLESS MYOCARDIAL INFARCTION IN PSYCHOTIC PATIENTS

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THAT infarction of the myocardium can occur without pain is a well established fact. To date there is no wholly satisfactory explanation for such occurrences, although several hypotheses merit consideration.[1-3] There are also differences of opinion concerning the frequency of painless myocardial infarction. In recent years clinical studies of both small and large series of cases with myocardial infarction have given the prevalence of painless cases as from less than 1 per cent[4] to a high of 38 per cent.[5] Most reports, however, cite a rate somewhere near 10 per cent.

The reason for such a large discrepancy primarily concerns each author's criteria for inclusion or noninclusion of cases in the painless group. Some omit sudden deaths whereas others include them; some include old infarctions, and others exclude them; some omit all patients who cannot give a clear history because of the presence of shock, uremia, diabetic acidosis, congestive heart failure or recent hemiplegia, and other authors include one or more of such cases in their statistics. Of course, another factor is the vigor with which pain is sought for when the history is taken.

I have found no reference in the literature to the question of whether painless myocardial infarction occurs in psychotic patients more or less often than in the general population. To determine the role of the presence of a psychosis the present study was undertaken.

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Background

Shortly after taking up my duties at the Veterans Administration Hospital, Bedford, Massachusetts, in 1946, I became aware that psychotic patients frequently did not react to painful pathologic processes as mentally normal persons did. My first impression was that this was mainly so in patients with organic psychoses, especially in those with general paresis, but it was not long before I realized that this was true for the patients with the functional psychoses. This became especially evident when patients with acute myocardial infarction were observed. Early in 1953 I gathered together the material to study the prevalence of painless myocardial infarction in psychotic patients.

Material

All records (clinical, post-mortem and electrocardiographic) in which the diagnosis of myocardial infarction, rupture of the myocardium or coronary thrombosis was recorded between 1947 and 1952 were studied. Altogether, one or more of these diagnoses were entered in the records of 99 patients. For the

sake of the study the cases were broken down into two classes: those in which the diagnosis was unconfirmed by either autopsy or electrocardiogram and those in which there was such a confirmation. For

TABLE 1. *Data in 99 Patients with the Diagnosis of Myocardial Infarction, Coronary Thrombosis or Cardiac Rupture.*

DATUM			NO. OF PATIENTS
Diagnosis Unconfirmed:			16
No autopsy or electrocardiogram			12
Autopsy			4
Cerebral hemorrhage		2	
Aortic thrombosis		1	
Dissecting aneurysm of superior mesenteric artery		1	
Diagnosis Confirmed:			83
Old myocardial infarction			32
By autopsy		12	
By electrocardiogram		20	
Acute myocardial infarction			51
By autopsy			17
Sudden death	12		
Rupture of myocardium & interventricular septum	5		
Clinically unsuspected	5		
Postoperative lobectomy	1		
Pneumonia	1		
Bronchogenic carcinoma	1		
Influenza	1		
Acute respiratory infection	1		
By electrocardiogram & autopsy		16	
By electrocardiogram		18	

inclusion in the study as a confirmed case from the electrocardiographic point of view, the criteria of Barker in his textbook, *Unipolar Electrocardiography*, were used (Table 1).

TABLE 2. *Ages of 51 Patients with Acute Myocardial Infarction.*

AGE GROUP	NO. OF CASES
yr.	
20-29	1
30-39	0
40-49	3
50-59	22
60-69	22
70-79	3

In the further analysis only the 51 patients with acute myocardial infarction are considered. Restriction of the analysis to the acute cases was considered to offer a more accurate evaluation of whether a patient did or did not have pain. However, it is impressive that none of the 32 patients with old myocardial infarctions had had an admission to the Acute Medical Ward for an acute episode that could have been interpreted as representing an acute myocardial infarction. This most probably signifies that these patients did not have signs or symptoms to bring them to the attention of a psychiatric aide, nurse or doctor — in other words, that they could well have represented cases of painless myocardial infarction.

The ages are shown in Table 2. The 1 patient in the group twenty to twenty-nine years of age was a twenty-seven-year-old schizophrenic man who had a myocardial infarction on the second day after a prefrontal lobotomy. Although he survived the myocardial infarction he succumbed a year later to viral encephalomyelitis (Guillain–Barré syndrome) with bulbar involvement. Post-mortem examination revealed an advanced arteriosclerotic process in all coronary arteries as well as a healed massive infarction of the anterior wall.

Although 79 per cent of the hospital population have the diagnosis of schizophrenia only 50 per cent of the patients with acute myocardial infarction carried this diagnosis (Table 3). The relatively high rate of myocardial infarction in the patients with

TABLE 3. *Mental Diagnoses in 51 Cases of Acute Myocardial Infarction.*

DIAGNOSIS		NO. OF CASES
Schizophrenic reaction		26
Paranoid	9	
Hebephrenic	9	
Catatonic	6	
Simple	1	
Mixed	1	
General paralysis of insane		7
Cerebral arteriosclerosis with psychosis		5
Alcoholic psychosis		5
Involutional melancholia		2
Manic-depressive psychosis		2
Miscellaneous mental disorders		4

general paralysis of the insane is interesting but unexplained.

Of interest are 4 cases with rupture of the left ventricle and a case of rupture of the interventricular septum (Table 4). Rupture of the myocardium as a

TABLE 4. *Site of 52 Acute Myocardial Infarctions in 51 Patients.*

SITE	
Anterior wall	16
Anteroseptal	8
Anterolateral	1
Posterior wall	12
Posterolateral	5
Anterolateral & posterolateral	1
Right coronary artery (thrombosis)	1
Left anterior descending artery (thrombosis)	2
Left recurrent artery (occlusion)	1
Rupture of myocardium (left ventricle)	4
Rupture of interventricular septum	1

cause of sudden death in previously undiagnosed cases of myocardial infarction is infrequent outside mental institutions,[6] as shown by Martland,[7] who found the rate of cardiac rupture as a cause of sudden death to

be only 2.1 per cent in the general population. In this hospital, from 1947 to 1952, there were 43 sudden deaths. Post-mortem examination was authorized in 24 of these cases, and in 5 rupture of the heart through a recently infarcted area was the cause of death — a frequency of 21.7 per cent. This high rate can only support the contention that myocardial infarction does occur without complaints of pain or other signs and symptoms that would bring these patients to the attention of alert and well trained personnel.

From Table 5 it is evident that the majority of cases of acute myocardial infarctions were picked up by alert psychiatric aides or nurses, who noted something wrong with the patient, rather than on the basis of complaints that were evaluated. Of further interest is the fact that 4 patients had a change in psychiatric behavior as their presenting sign. It is usually the overactive or mentally disturbed patient who suddenly becomes docile or quiet who is suspected of having some acute medical or surgical illness, and in the 4 cases cited this proved to be acute myocardial infarction.

TABLE 5. *Presenting Signs and Symptoms of 52 Acute Myocardial Infarctions in 51 Patients.*

INDICATION OF INFARCTION	NO. OF CASES
Weak spell or collapse	9
Chest pain	7
Dyspnea or tachypnea	4
Change in psychotic behavior	4
Cyanosis	3
Loss of consciousness	2
Vomiting or pyrosis	2
Unsteady gait	2
Pallor	2
None	2
Malaise	2
Right-lower-quadrant pain	1
Sudden death	12

Two of the 51 patients had no signs or symptoms of an acute myocardial infarction; the diagnosis was made by sheer chance. One of the 2 patients is described below in a case report. In the other patient, who was convalescing from a subtotal gastrectomy, frequent electrocardiograms were done at the request of the surgeon to evaluate the approximate serum potassium level. On one of these routine checks it became evident that the patient had had an acute myocardial infarction — without complaint of any sort from the patient or any sign that could have been interpreted as indicating an acute episode.

The increase in the frequency of pain noted in Table 6 as compared to Table 5 was considered to be partly due to suggestive questioning of the suggestible patients, although it must be further noted that in the days after the first twenty-four hours no other patient gave a history of pain.

CASE REPORTS

CASE 1. A 44-year-old man with a diagnosis of paranoid schizophrenia had known hypertension since 1950 and in 1951 had sustained a cerebrovascular accident, with resultant right-sided hemiplegia, after electroshock therapy.

In the summer of 1952 one of the physicians on the Medical Service was looking for patients — mute or partially mute patients — for a study of the effect of sodium amobarbital (Amytal) on mutism. This patient was chosen to participate in the study, and in preparation for this an electrocardiogram was taken late in the afternoon of July 8 that was interpreted as consistent with a fresh posterior-wall infarction after it was brought to my office on July 11. In the intervening days nurses, aides and physicians had noted nothing wrong with the patient, and his psychotic behavior had not altered. Over the week end, too, he had been visited by his sister who had told the nurse that her brother looked well to her.

TABLE 6. *Most Frequent Signs and Symptoms during the First Twenty-Four Hours in 51 Patients with 52 Acute Myocardial Infarctions.*

INDICATION OF INFARCTION	NO. OF CASES
Chest pain	13
Dyspnea	10
Shock syndrome	9
Nausea or vomiting	9
Cyanosis	7
Weakness	5
Weak spell	5
Collapse	4
Change in psychotic behavior	4
Pallor	4
Sudden death	12

On Monday, July 11, the physical examination was negative except for the neurologic residua of the old hemiplegia. During the next few days the electrocardiograms showed extension of the infarction to involve the lateral wall of the left ventricle, but the original insult as well as the extension was without pain or other signs or symptoms.

On July 11 the white-cell count was 10,000, with 75 per cent neutrophils. The sedimentation rate was 12 mm. per hour.

After the electrocardiograms had stabilized, the patient was returned to his own medical ward, where he suddenly died on October 12.

Post-mortem examination revealed a healed posterior-wall infarct, with involvement of the lateral portion of the left ventricle and with a superimposed fresh myocardial infarction.

CASE 2. A 55-year-old man with simple schizophrenia was sent to the Acute Medical Ward despite his claims of feeling well, because his nurse and doctor had noted him to be dyspneic and cyanotic and his heart rate to be 140 per minute.

On arrival at the Medical Ward, after having insisted on walking there from his building, the patient was intensely cyanotic but was only slightly dyspneic. He was placed in an oxygen tent immediately despite his claims of good health; physical examination revealed a heart of a normal size with good heart sounds, no murmurs or friction rubs and a pulse of over 200. The radial pulse and blood pressure were not obtainable. The clinical impression was that the patient had either atrial or ventricular tachycardia.

An electrocardiogram was taken immediately, showing a

ventricular tachycardia of 240 per minute. The white-cell count was 12,000, with 72 per cent neutrophils.

Treatment with quinidine was started, and after a total of 1.5 gm. had been given by mouth in 6 hours, normal sinus rhythm was re-established. The electrocardiogram confirmed this and in addition revealed an extensive fresh anterior-wall infarction from which the patient made an uneventful clinical recovery, never having experienced pain.

CASE 3. A 53-year-old man with catatonic schizophrenia was admitted to the Acute Medical Ward on March 13, 1951, in a comatose state.

A review of the clinical record, which dated back to 1928, when he was first admitted to the hospital, revealed no previous major illnesses and no abnormalities in the yearly examinations of blood or urine. The blood pressure had been normal for years.

On the morning of March 13, while brushing his teeth, he suddenly slumped and fell backward into the arms of a psychiatric aide. He could not be aroused; the extremities were rigid, and his color was poor.

Within several minutes he was seen by his ward physician, who noted a good pulse at a rate of 80 per minute, a blood pressure of 110/70 and clear lungs. However, neurologic examination showed bilateral pin-point pupils, absent corneal reflexes, loss of all superficial reflexes, bilateral positive Babinski signs and deep tendon reflexes that were sluggish in the upper and hyperactive in the lower extremities. The patient responded by feeble motions to painful stimuli on the right, but not on the left.

He was catheterized, and the urine obtained was normal on examination. The white-cell count was 9800, with 73 per cent neutrophils. The nonprotein nitrogen was 23 mg. per 100 cc. A lumbar puncture revealed clear spinal fluid under normal pressure; the cell count and total protein were within normal limits.

Despite the definite impression that the patient had sustained a cerebral hemorrhage, the physician, being aware of the bizarre clinical picture that is often presented by mental patients with myocardial infarction, took an electrocardiogram, which revealed a fresh posterolateral myocardial infarction.

Shortly after admission the patient began having Cheyne–Stokes respirations, and the temperature rose to 106°F. during the night. Twenty hours after admission early pulmonary edema was evident, but despite rapid digitalization, this progressed rapidly and he died 22 hours after admission, never having aroused from his comatose state.

Post-mortem examination revealed a fresh thrombus in the left descending coronary artery, with infarction of the posterolateral wall. The brain gave no evidence of hemorrhage.

CASE 4. A 55-year-old man with general paresis and choreoathetotic movements of all extremities was admitted to the Acute Medical Ward on May 5, 1947, for study after his ward physician, that morning, had found him pulseless. In the 3 previous days he had had 3 grand-mal epileptiform seizures, the first on record for him since his admission to the hospital 19 years before. These seizures were considered due to his general paralysis, and his physician had planned to refer him to the neurologist for consultation the following week. In the meantime, daily examinations showed nothing unusual, the patient carrying on in his usual fashion. On the morning of admission the radial pulse was absent, and the blood pressure unobtainable although he appeared in no distress. On admission the temperature was 100.6°F., the respirations 20, and the pulse approximately 160 per minute; the blood pressure was 60/40. The lungs were clear. The heart was not enlarged, but the heart sounds were of poor quality with a tick-tock rhythm. A Grade 2 systolic murmur was heard over the pulmonic area.

The diagnosis was ventricular tachycardia, and myocardial infarction was suspected. The white-cell and differential counts, as well as the sedimentation rate, were normal. An electrocardiogram showed the presence of ventricular tachycardia.

The patient was placed in oxygen and started on quinidine, 0.2 gm. every 2 hours for 36 hours, with no effect. This was then stepped up to 0.2 gm. every hour without reversion of rhythm to normal. Intravenous injection of magnesium sulfate was then tried, also without success. On the 3d day after admission 1.2 mg. of atropine was given subcutaneously in divided doses, and 45 minutes later the rhythm reverted to normal. An electrocardiogram 4 minutes after reversion showed a fresh infarction of the posterior wall of the myocardium.

Recovery was uneventful. At no time during the illness did the patient complain of pain or appear in any distress.

DISCUSSION

When the presenting symptoms are considered and the cases of sudden death excluded, painless myocardial infarction occurred in 82.5 per cent of the cases studied. The rate fell to 67.5 per cent when the symptoms during the first twenty-four hours were analyzed. These figures are in sharp contrast to the much lower frequency of painless myocardial infarction noted in published papers. A history, especially in an acute illness, is often obtained from psychotic patients. Even in psychiatrically mute patients a history can often be obtained with intravenous administration of sodium amobarbital. Occasionally, the history given is so bizarre that it defies interpretation by the physician. However, this accounts for only a small number (approximately 5 to 10 per cent) of painless myocardial infarctions in psychotic patients. In my opinion the *meaning* of pain is lost to the majority of patients with psychoses both organic and functional. The situation is not unlike that in mentally normal patients after lobotomy for the relief of pain, who, having sustained organic damage to the frontothalamic radiations by surgery, show an unchanged or lowered threshold for pain in test situations and yet obtain relief of pain from a painful pathologic process.[8] This paradoxical situation has been explained as being due to the loss of the *meaning* (or emotional component) of pain, and therefore, with the *meaning* of pain lost, the patient does not respond in the usual manner to painful stimuli.

I believe that psychotic patients, although they perceive painful sensations, do not react to the pain because of the fact that the meaning of pain is actually lost to them. In patients with organic psychoses it can be speculated that the loss of the meaning of pain lies in organic damage to the frontal lobes. It is interesting that the patients with general paresis, in my experience, are notoriously the ones who have no pain in pathologic states ordinarily painful. In this disorder the damage is diffuse throughout the cortex. Fulton[9] has noted, "it is the general impression of neurosurgeons that the extent to which pain is relieved (with prefrontal lobotomy) depends not so much upon the location of the lesion as upon the amount of cortical tissue from which projections are interrupted." In the patient with general paresis a great deal of cortical tissue is damaged. In patients with functional psychoses, it can also be speculated that diffuse damage to cortical cells by biochemical or enzymatic agents could account for the loss of meaning of pain in a great majority of these patients.

Summary

A study of the frequency of painless myocardial infarction in psychotic patients showed that when cases of sudden death were excluded, pain was absent in 67.5 per cent; when cases of sudden death were excluded and only the presenting symptomatology taken into account, pain was absent in 82.5 per cent.

Data on the 51 patients with 52 acute myocardial infarctions are presented.

Among 12 cases of sudden death in the series the cause of death was rupture of the heart in 4 cases and rupture of the interventricular septum in 1.

A change in psychotic behavior was the presenting sign in 4 patients with acute myocardial infarction. In 2 other patients no signs or symptoms were evident, the infarction being detected by routine electrocardiograms accomplished for other studies.

Four case reports of psychotic patients with acute myocardial infarction are presented.

To explain the frequency of painless myocardial infarction in psychotic patients the *meaning* of pain is believed to be lost to these patients, who are left nonresponsive to painful processes.

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MERCURIALISM*

Report of a Case Due to Oral Ingestion of a Mercurial Diuretic

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THE many years of clinical experience with mercurial diuretics have established these drugs as effective and relatively nontoxic.

Although the literature contains many reports of toxicity from parenteral administration of mercurial medication there are few reports of toxicity resulting from the use of mercurial diuretics given by mouth. Batterman, DeGraff and Shorr[1] described early mercurialism in 3 patients using mercurophylline (Mercupurin)§ by mouth. This was manifested by gastrointestinal symptoms and increasing albuminuria. One of these patients had severe gingivitis and an elevation of blood nonprotein nitrogen to 52 mg. per 100 cc. A fourth patient showed an elevation of nonprotein nitrogen to 112 mg. per 100 cc. These elevated determinations were thought to be due to the use of mercurial diuretics, although all the patients had pre-existing renal disease. Symptoms and azotemia disappeared after withdrawal of the medication.[1]

In the recent reports on the use of chloromerodrin¶ (Neohydrin) the only toxic findings mentioned are gingivitis and gastrointestinal disturbances.[2,3]

In the case reported below, the signs and symptims of subacute mercurial poisoning followed the use of chloromerodrin.

Case History

A.R., a 73-year-old practical nurse, was admitted to the hospital on August 13, 1953, complaining of a severe sore throat. For thirty years she had had mild hypertension. In July, 1952, she sought medical attention for edema of the lower extremities and received 6 injections of meralluride (Mercuhydrin).‖ In September of the same year she was admitted to another hospital because of pneumonitis, atrial fibrillation and congestive heart failure; examination of the urine was within normal limits, with a specific gravity of 1.020. The blood nonprotein nitrogen was 34 mg. per 100 cc. She received antibiotic therapy, sodium-restricted diet, digitalis and 2 injections of mercaptomerin (Thiomerin) and was discharged on a sodium-restricted diet, digitalis and a daily tablet of chloromerodrin. She was seen at frequent intervals by her physician, who found no abnormalities, and she was given no mercurial diuretics parenterally. In January a nonpruritic macular rash developed, lasting 2 weeks, for which no medical attention was sought. By March it was thought that progress permitted visits to be spaced at 3-month intervals. She continued her therapy meticulously. Her only complaint was slight anorexia, which persisted until admission. Four weeks before admission she thought that she could taste the gold fillings in her teeth. Two weeks later she complained of a dull ache ("like a

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§Each tablet contained 100 mg. of Mercupurin powder, equivalent to 30 mg. of mercury and 27 mg. of anhydrous theophylline.

¶Each tablet contains 18.3 mg. of 3-chloromercuri-2-methoxypropylurea.

‖A methoxyoximercuripropylsuccinylurea.

neuralgia") circumorally. Her gums ached to the extent that she curtailed toothbrushing and started the use of a commercial mouthwash. At about this time she noted the onset of increased salivation. Six days before admission she saw a light-ashen-gray area on the inner surface of the right side of the lower lip. Two days later a sore throat of increasing severity developed and in 2 more days swollen, tender anterior cervical lymph nodes and mild dysphagia had appeared. She therefore sought hospitalization.

On entry she appeared sallow. Speech was impaired by salivation. She was oriented, but her mental responses were dull. The temperature was 101.5°F. by mouth. The skin was dry. A foul odor emanated from the mouth. There was a necrotic area about 2 cm. in diameter on the inner surface of the lower lip, another on the undersurface of the tongue, both on the right side, and a similar shaggy area on the right anterior pillar. There was a grayish exudate about the teeth, with a blue-black deposition at the alveolar margin. The gums were tender and swollen and bled easily. The respiratory rate was 24, and there were coarse breath sounds posteriorly at both bases. The heart was enlarged, the border of cardiac dullness extending 3 cm. to the left of the midclavicular line, with the point of maximal impulse in the 6th interspace. A harsh, high-pitched Grade 3 systolic murmur was heard at the apex radiating over the entire precordium, up the neck and to the back. Atrial fibrillation was present, with an apical rate of 130 and a pulse deficit of 30. The liver and spleen were both palpable 2 fingerbreadths below the costal margins. The anterior cervical lymph nodes measured 1 or 2 cm. in diameter and were tender, firm and easily movable. There was + pitting pedal edema bilaterally. Neurologic examination was negative except for the state of consciousness.

Specific gravities of random specimens of urine were 1.005 to 1.010. On an overnight concentration test performed by restriction of all fluids from 5 p.m. to 8 a.m. the next day, the specific gravity was 1.014. The pH was repeatedly acid, and albumin was not detectable except in 1 sample, in which a trace was found. Sugar, acetone and bile were not detectable in the urine. The sediment on admission showed 10 to 13 red cells, 5 white cells and an occasional granular cast per high-power field. These findings had cleared on discharge. A phenolsulfonphthalein test disclosed 30 per cent excretion of the dye in 1 hour and 10 per cent in the 2d hour. The urinary mercury level 2 weeks after the patient had been off all mercurial medication was 1.7 mg. per liter by the method of Storlazzi and Elkins.[4*]

Examination of the blood revealed a hematocrit of 34 per cent. The white-cell count was 7500 with 88 per cent neutrophils, of which 12 per cent were band forms and 20 per cent lymphocytes. The blood sugar (fasting) was 113 mg. per 100 cc.; the chloride was 109 milliequiv., the sodium 141 milliequiv., and the potassium 4.8 milliequiv. per liter. The carbon dioxide combining power was 40 vol. per cent. The total serum protein was 4 gm. per 100 cc. and was the same 2 months later (normal, 5.5 to 6.5 gm.). The blood nonprotein nitrogen, which was 75 mg. per 100 cc. on admission, had risen to 95 mg. 2 days later, declining to 57 mg. in 2 weeks and to 37 mg. at discharge; 2 months later it was 35 mg. per 100 cc. The formol-gel test was negative, and cephalin flocculation was + in 48 hours. Two blood cultures were negative, and no pathogens were found in a throat culture.

The basal metabolic rate was +8 per cent. An electrocardiogram confirmed the atrial fibrillation. X-ray examination showed changes in the lungs suggestive of congestive heart failure and an enlarged heart; minimal Paget's disease of the femoral heads and generalized osteoarthritis were also noted.

On admission the patient was given 2 cc. of mercaptomerin, a sodium-restricted diet, digitalis and 900,000 units of aqueous penicillin. No mercurial medication was given after this time. The necrotic area in the mouth cleared within 3 or 4 days, leaving only a residual hyperpigmented bluish mark. Within 3 days she was afebrile, and the radial pulse deficit had decreased to 5 per minute.

During the next 2 weeks she became more mentally alert, and the nodal tenderness, salivation, metallic flavor and foul odor from the mouth disappeared. However, ankle edema increased slightly.

*Performed by Mr. J. P. Fahey, of the Division of Occupational Hygiene, Department of Labor and Industries, Commonwealth of Massachusetts.

Discussion

The symptoms that may be present in chronic mercury poisoning are stomatitis, colitis, progressive renal damage, loss of appetite, nutritional disturbances, anemia and nervous-system manifestations characterized by behavioral changes, peripheral neuritis, depressions, insomnia and hallucinations. In the subacute form the nutritional and nervous-system manifestations are not severe.[5]

This patient demonstrated a mercurial stomatitis as evidenced by the sore gums, ashen-gray lesions of the buccal mucosa, increased salivation, metallic taste and blue-black "mercury line." Heavy-metal lines are most easily seen in association with poor oral hygiene. This serves to accelerate the appearance of the line by providing the sulfides that combine with the heavy metal to be deposited on the gums.[6,7]

Except for the loss of appetite gastrointestinal symptomatology was not a factor in this case.

The laboratory data are consistent with a toxic process in the kidneys. The blood nonprotein nitrogen a year before admission was within normal limits, but it was high at the time of admission, falling after withdrawal of mercurial products. It seemed unlikely that congestive heart failure caused the azotemia because the pulse deficit decreased in the first few days when the nonprotein nitrogen was rising, and the nonprotein nitrogen fell at a time when the edema of the lower extremities became more marked and declined to normal when the edema was more severe. The low specific gravity, the low phenolsulfonphthalein excretion and the hypoalbuminemia are also consistent with a toxic process in the kidneys. Although Martin and Reid[8] report that hypoproteinemia apparently protected a limited series of animals against mercuric chloride poisoning, Diengott[9] suggests that hypoalbuminemia may be a factor in causing toxic reactions and has described hypoalbuminemia in patients who died suddenly after being given intravenous injections of mercurial diuretics.

A single dose of chloromerodrin has been found to be fully excreted within ninety-six hours.[10] Long-term urinary-excretion studies with chloromerodrin have not yet become available; the value of 0.25 mg. of mercury per liter, considered to be indicative of hazardous exposure in industry,[11] was used as a basis for comparison. This patient showed an excretion of 1.7 mg. per liter two weeks after all mercurial products had been discontinued.

No explanation can be offered for the prolonged excretion of mercury in the urine after a minimal dosage. Wilson and Holzel[12] found that, although manifestations of nephrosis caused by use of mercuri-

al teething powders in young children cleared after the powders were withdrawn, there was a persistently high urinary excretion of mercury. Moyer et al.[10] showed that urinary mercury values increased as ingestion of chloromerodrin was sustained. However, in dogs on chloromerodrin for a year or longer little tissue retention of mercury was noted, and the conclusion was drawn that only small amounts of mercury should be present in the urine of patients who have been off the drug for two weeks.[13]

Summary and Conclusions

Subacute mercury poisoning from oral administration of a mercurial diuretic is reported. The patient demonstrated sore gums, ashen-gray lesions of the buccal mucosa, a blue-black mercury line on the gums, mental dullness and a transient elevation of the blood nonprotein nitrogen consistent with renal damage.

The possibility of mercury poisoning must be considered when prolonged therapy with mercurial diuretics by mouth is instituted, although it is presumably rare. Frequent examinations of the urine and blood nonprotein nitrogen determinations are recommended during treatment.

We are indebted to Dr. Edward Kass, of the Thorndike Memorial Laboratory, Boston City Hospital, for help in preparing the manuscript, and to Dr. Charles Prizer, of the South Department, for encouraging the publication of this case report.

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EFFECT OF *l*-TRI-IODOTHYRONINE ALONE AND COMBINED WITH *l*-THYROXINE IN NONMYXEDEMATOUS HYPOMETABOLISM*

Preliminary Report

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BOSTON

THE dramatic relief of the clinical manifestations of myxedema by the administration of desiccated thyroid is a striking example of the efficacy of hormone replacement therapy. Many patients are seen, however, with persistently low basal metabolic rates¶ and with symptoms usually associated with thyroid deficiency (muscle or joint aching or stiffness, chronic fatigue, lethargy, facial or periorbital puffiness), in whom the administration of large doses of thyroid or *l*-thyroxine does not elevate the basal metabolic rate or relieve the symptoms. We have considered the possibility that such patients are unable to utilize — that is, to absorb, convert to an active form or metabolize it — *l*-thyroxine. This concept suggested the investigation of the effects of another potent thyroid substance, *l*-3-5-3′ tri-iodothyronine, in such patients. The beneficial results of its administration alone or in combination with thyroxine in 2 patients previously unresponsive to large doses of desiccated thyroid or *l*-thyroxine warrant this preliminary report.

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¶Known causes of hypometabolism such as adrenal insufficiency, starvation, anexoria nervosa and nephrosis are excluded.

Methods

Measurements of basal metabolic rate were made in duplicate with a Collins–Benedict–Roth apparatus using the Dubois normal standards modified by Boothby and Sandiford. These determinations were made at intervals of approximately a week to obtain a reliable base line before any change in medication. Serum cholesterol was determined by the method of Sperry and Schoenheimer,[1] and protein-bound iodine by the method of Barker et al.[2] The twenty-four hour uptake of I^{131} by the thyroid gland was measured by a method previously described in this laboratory.[3]

Case Reports

Case 1. R.B., a 29-year-old man, had suffered from a "tired and logy" feeling for 3 or 4 years. His physician had prescribed increasing doses of desiccated thyroid and during the 2 years before study, 5 gr. (0.3 gm.) had been adminis-

tered daily. On this dosage the patient complained of insomnia, palpitation, warmth and perspiration; the basal metabolic rate was −20 per cent; the serum cholesterol was 187 mg. per 100 cc., and the 24-hour thyroid uptake of a tracer dose of I^{131} was 5 per cent.

During the next 6 months, after all medication had been omitted, the basal metabolic rate varied from −26 to −30 per cent. The 24-hour uptake of I^{131} by the thyroid gland was 33 per cent. The patient still complained of a dull feeling and tiredness. Again, 10 months later, still without thyroid medication, the basal metabolic rate was −25 per

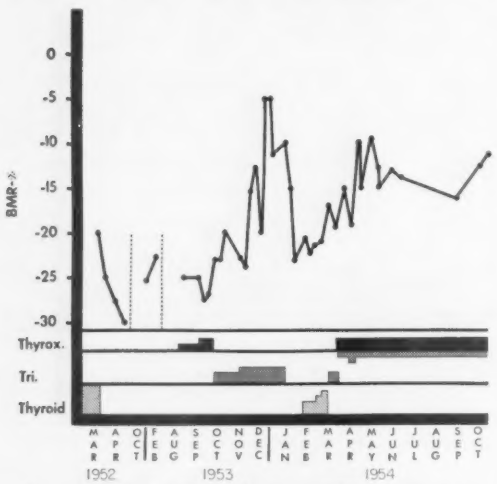

FIGURE 1. *Basal Metabolic Rate (BMR) in Case 1.*

cent; the serum cholesterol ranged from 227 to 253 mg. per 100 cc. The serum protein-bound iodine was 5.0 microgm. per 100 cc.

The experimental data are presented in Figure 1. *l*-thyroxine,* 0.1 mg. daily for 4 weeks and 0.2 mg. daily for the subsequent 3 weeks, did not alter the clinical state. The basal metabolic rate averaged −25 per cent, and the serum cholesterol remained 227 mg. per 100 cc. The *l*-thyroxine was omitted, and the next day, 70 microgm. of *l*-tri-iodothyronine was started and continued daily for 4½ weeks. There was only a slight rise in the basal metabolic rate; the cholesterol was 226 mg. per 100 cc. The dosage was increased to 105 microgm. daily; during the ensuing 35 days the basal metabolic rate progressively increased to −5 per cent. The serum cholesterol fell only slightly — to 195 mg. per 100 cc.

During this period, the patient was alert and active and stated that he felt "normal." After 3 weeks on this regimen, during which the basal metabolic rate was maintained at −5 to −10 per cent, all medication was omitted. One week later a placebo (resembling the tri-iodothyronine tablet) was administered. The basal metabolic rate fell promptly on omission of the tri-iodothyronine and 3 weeks later was −23 per cent; the serum cholesterol rose to 242 mg. per 100 cc. The clinical change induced by the omission of tri-iodothyronine and the substitution of placebo medication was striking. The patient complained of severe lethargy, fatigue and puffiness of the eyes. At this time, 2 gr. (0.12 gm.) of desiccated thyroid was administered daily for 14 days and 3 gr. (0.2 gm.) for an additional 7 days, without effect on the clinical condition or basal metabolic rate; 4 gr. (0.25 gm.) for an additional 7 days produced only a slight rise in the basal metabolic rate, from −21 to −17 per cent. After the desiccated thyroid had been omitted 70 microgm. of *l*-tri-iodothyronine for 14 days failed to raise the basal metabolic rate further. For 2 weeks thereafter 0.2 mg. of *l*-thyroxine was administered in combination with 35 microgm. of *l*-tri-iodothyronine. The basal metabolic rate began to rise. An additional 35 microgm. of the latter (that is, 70 microgm. of tri-iodothyronine combined with 0.2 mg. of thyroxine) for 8 days caused a further increase in the rate. The patient complained of insomnia, nervousness, weakness, sweating and increased appetite. The dosage was cut to 35 microgm. The basal metabolic rate remained elevated, but the symptoms of thyroid toxicity subsided, and he felt well. On 25 to 35 microgm. of *l*-tri-iodothyronine and 0.2 mg. of *l*-thyroxine daily, the basal metabolic rate has remained between −12 and −5 per cent for 7 months, and the clinical improvement has been sustained.

CASE 2. W.G., a 38-year-old man, was first examined in 1944 because of aching in both knees. He gave a history of previous sluggishness and low basal metabolic rate (−40 per cent), for which he had been on a regimen of 2 to 4 gr. (0.12 to 0.25 gm.) of desiccated thyroid for the previous ten years. Four of his maternal aunts were known to be hypometabolic, with basal metabolic rates of approximately −20 per cent. All presented skin pallor and facial puffiness, and several complained of fatigue and aching joint pains; however, none were considered hypothyroid clinically, and several had taken desiccated thyroid without relief of symptoms and without change in basal metabolic rate. Physical examination of the patient in 1944 was completely negative except for facial pallor and pastiness. The basal metabolic rate was −19 per cent. Thyroid was omitted. Over the course of the next 10 years he was seen infrequently with similar complaints. In 1945 the basal metabolic rate was −19 per cent, and the cholesterol 245 mg., and the cholesterol esters 184 mg. per 100 cc. In 1952 the basal metabolic rate was −21 per cent, and the protein-bound iodine was 6 microgm. per 100 cc. Examination of the blood and urine was negative; an electrocardiogram showed a sinus rhythm, with a normal PR interval and QRS volt-

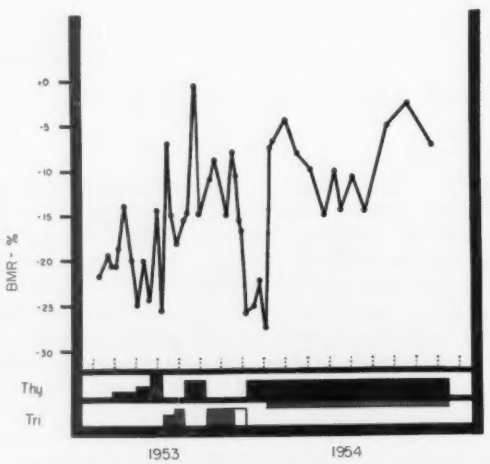

FIGURE 2. *Basal Metabolic Rate (BMR) in Case 2.*

age and width. In July, 1953, on routine examination, the patient described himself as feeling "quite normal." On physical examination there was slight periorbital puffiness; the skin and hair had normal texture, and the hands were cool and moist. The basal metabolic rate was −20 per cent. The serum cholesterol was 246 mg. per 100 cc.

The clinical data are presented in Figure 2. *l*-thyroxine, 0.1 mg. daily, was administered for 38 days, 0.2 mg. for 18 days, and 0.4 mg. for 14 days. There was no significant change in the basal metabolic rate, serum cholesterol or clinical condition. *l*-tri-iodothyronine, 70 microgm. daily for 21 days, was similarly without clear effect on basal metabolic rate or serum cholesterol; an increase to 105 microgm. daily for the subsequent 15 days was also without effect.

*l-thyroxine (Elthrin) and tablets of *l*-tri-iodothyronine were generously supplied by Smith, Kline and French Laboratories, Philadelphia.

The substitution of 0.3 mg. of thyroxine daily for 27 days immediately after this dose of tri-iodothyronine resulted in a rise of the basal metabolic rate to −1 per cent. When *l*-thyroxine was omitted and replaced by 105 microgm. of *l*-tri-iodothyronine the basal metabolic rate averaged −12 per cent for the next 6 weeks. When a placebo (open square in Fig. 2) was then substituted the basal metabolic rate fell to −25 per cent, remaining at that level during the ensuing 24 days while 0.3 mg. of *l*-thyroxine was administered daily. During this period, increased dullness, pallor and fatigability were noted. The addition of 35 microgm. of *l*-tri-iodothyronine daily to the regimen of 0.3 mg. of *l*-thyroxine was followed by a rise in the basal metabolic rate to −5 per cent. During the ensuing 7 months on this combination, the basal metabolic rate has averaged −8.0 per cent (range, −2 to −15 per cent). Although he had initially considered himself "quite normal" he volunteered the statement that in retrospect there had been a definite sense of well being and increased vigor and alertness during the period of combined therapy.

Discussion

The clinical and metabolic response to *l*-tri-iodothyronine and to combinations of that compound and thyroxine was striking in these 2 patients presenting the clinical features of nonmyxedematous hypometabolism. The conclusion that such patients are not myxedematous has rested on their unresponsiveness to desiccated thyroid as well as on the demonstration of normal parameters of thyroid function other than oxygen consumption. The symptoms described by these and other such patients, including mild puffiness and obesity, lethargy, fatigue and muscular and joint stiffness, have frequently been labeled psychogenic when they failed to respond to the administration of desiccated thyroid.

It is of considerable interest, therefore, that the basal metabolic rate in these 2 euthyroid hypometabolic patients was clearly elevated by the oral administration of *l*-tri-iodothyronine alone and in combination with *l*-thyroxine. Moreover, striking clinical improvement accompanied the rise on *l*-tri-iodothyronine. In Case 1, 105 microgm. of *l*-tri-iodothyronine daily raised the basal metabolic rate from −25 per cent to −5 per cent whereas 0.3 gm. of desiccated thyroid had previously failed to elevate it above −20 per cent. In other studies in man[4,5] *l*-tri-iodothyronine has been shown to be three or four times as active metabolically as *l*-thyroxine, and 0.1 mg. of *l*-thyroxine to be roughly equivalent to 1 gr. of desiccated thyroid. On the basis of such data 105 microgm. of tri-iodothyronine could be considered the approximate equivalent of 3 or 4 gr. of desiccated thyroid.

The effectiveness of combinations of *l*-thyroxine and *l*-tri-iodothyronine in these 2 patients was also of interest. In Case 1, 0.25 gm. of desiccated thyroid did not raise the basal metabolic rate above −17 per cent and had little clinical effect; on the other hand 0.2 mg. of *l*-thyroxine administered simultaneously with 25 to 35 micrograms of tri-iodothyronine raised the metabolism to −12 per cent and relieved the symptoms of hypometabolism for seven months at the date of writing. In Case 2, 0.4 mg. of *l*-thyroxine failed to elevate the basal metabolic rate above approximately −20 per cent, and 70 microgm. of *l*-tri-iodothyronine alone was likewise ineffective. The administration of 0.3 mg. of *l*-thyroxine immediately after fifteen days of 105 microgm. of *l*-tri-iodothyronine daily elevated the basal metabolic rate to −5 per cent. Subsequently, 0.3 mg. of the former and 25 to 35 microgm. of the latter each day maintained the rate at −5 to −12 per cent, and this metabolic change was accompanied by clinical improvement lasting seven months at the time this paper was submitted for publication.

Various explanations for the therapeutic results in these 2 cases have been considered. These include, first of all, a defect in the absorption of *l*-thyroxine or desiccated thyroid from the gastrointestinal tract; in contrast, *l*-tri-iodothyronine may be more readily absorbed; investigations of the absorption of these hormones from the gastrointestinal tract and comparisons of oral and parenteral administration are in progress. Secondly, the deiodination of thyroxine (tetraiodothyronine) to tri-iodothyronine, which may represent the active form of the thyroid hormone, may have been deficient. Impaired permeability of the tissues of such patients to thyroxine but not to tri-iodothyronine is another possibility. Finally, deficiency of tri-iodothyronine, which may be required for optimum metabolism of thyroxine, may have been present. The observed effectiveness of a combination of tri-iodothyronine and thyroxine or of thyroxine immediately after a dosage of tri-iodothyronine, as in Case 2, when each administered alone was previously ineffective, is consistent with this hypothesis.

The site of production of tri-iodothyronine and its role as a thyroid hormone in metabolism have not yet been conclusively demonstrated. The pathogenesis of nonmyxedematous hypometabolism remains obscure. The observations presented above have raised interesting questions regarding the nature of this syndrome and the role of tri-iodothyronine in thyroid physiology that will require further investigation.

Summary

The striking clinical and metabolic response that followed the oral administration of *l*-tri-iodothyronine (105 microgm.) alone or in combination with *l*-thyroxine (25 to 35 microgm. of tri-iodothyronine and 0.2 to 0.3 mg. of *l*-thyroxine) is reported in 2 patients with the clinical syndrome of nonmyxedematous hypometabolism. These patients were previously unresponsive to the oral administration of larger doses of desiccated thyroid or *l*-thyroxine. Various possibilities concerning the nature of non-myxedematous hypometabolism and the mechanism of tri-iodothyronine in this syndrome are considered.

We are indebted to Dr. Haskell S. Ellison for his helpful participation in the early phases of the studies.

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SPECIAL ARTICLE

LUCUBRATIONES

An Analysis of Two Hundred Night Calls

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IT is told that before the invention of the telephone a large Boston hospital had a communication system that in the house officers' quarters consisted of six speaking tubes, each with a bell that could be jangled with a cord. One night the supervisor inadvertently jangled the six bells together, and shortly six tired voices simultaneously ordered, "Give him a quarter of morphine."

It does often seem that the administration of morphine allays practically all the ills of the night. If that is true, how great an easement to the combined effort of responding to the night call and of struggling with the diagnosis it would be to realize, after the tintinnabulation of the telephone, that all that is needed beyond one's physical presence is a syringe and 1 cc. of morphine sulfate solution!

It was thought to be of some interest to see if night therapeutics is as automatic as the foregoing paragraphs suggest. Furthermore, it seemed likely that a tabulation of nighttime diseases would be a help in diagnosis by probability.

Making a tentative diagnosis based solely on the probabilities raised by the obvious variables of age, sex, season and so forth is a method of convenience and also an interesting pastime. This is an attempt to determine whether the single factor of a call made during the night could perhaps in itself establish a helpful set of probabilities.

To anticipate, no very definite pattern of diagnoses emerged. There is, however, an even probability that if the telephone rings while the physician is asleep (during the conventional hours) he can be assured that he is being called upon to deliver a new life, to pronounce the passing of one or to treat biliary-tract disease, respiratory infection or injury. Other than this, a heterogeneous group of illnesses present themselves.

Definitions

Two hundred consecutive night calls were analyzed for the purpose of this study. Some definitions of various aspects of a "night call" are necessary. The rare cases in which a patient was satisfied with advice over the telephone, eagerly proffered and ordinarily as eagerly refused, are omitted. "Night" is defined, not too arbitrarily, as the span from 11:30 p.m. to 8:00 a.m. This period begins after the early-evening calls have been attended to (the head of the family having returned home to take charge), ends before the morning telephone hour begins and is a time that should be quiet except for real emergencies.

A "call" is attendance on a patient (or group of patients) in the home, hospital, office, street or wherever he is taken sick. Calls that originated before 11:30 p.m. but wore on into the night later than this are not included.

The practice from which this series was derived is a general (family-type) practice including obstetrics but not surgery and located in a semirural community of 4000 population. It involved availability for accident calls at the local hospital four weeks in each ten-month period.

Of the series 68 were hospital calls, 14 were in the office (the office is located in the home), 1 on the highway, and 1 at the State Police Barracks. The house calls naturally made up the great bulk of the series; there were 116 of these.

Of the hospital calls, 13 were made on accident service, and 55 for private patients. Accident-call patients were, of course, largely victims of automobile misadventures in the vicinity. There were 15 of them, and they had the expected lacerations and fractures. Patients with amnesia, postepilectic stupor and diabetic ketosis were also encountered on the streets.

Services to private hospital patients were largely those of delivery or pronouncing a person dead. Of the 55, 44 were for the former, and 6 for the latter. There were 2 cerebrovascular accidents, 2 first assists and 1 catheterization.

Of the office callers 6 had minor traumatic lesions, 3 minor respiratory infections, and 2 postexodontia bleeding. The other 4 suffered from a felon, hives, gastroenteritis and alcoholic intoxication.

The highway episode was the care of an elderly person in a confused state who was wandering about. The call to the State Police Barracks was made in response to a request for help in commitment.

Diagnostic Classification

Diagnostically, all 200 calls were grouped as surgical, medical, obstetric or dead on arrival. Many conditions, of course, could be classed in different ways according to taste. The distinction between medical and surgical cases is occasionally slight, and here the criterion used was operability. Thus, carcinoma with metastases and mesenteric thrombosis, in extremis, were classed with the medical calls. Conditions ordinarily handled successfully with antibiotics, such as otitis, and conditions for which the treatment is ordinarily medication, such as dysmenorrhea, were also grouped with the medical cases. The relative proportions of these groups are shown in Figure 1.

Types of Cases

So far as sex and age distribution go, the female and the middle-aged groups predominated. One hundred and nineteen patients were female and 86 male. By age group 61 per cent were between 15 and 60

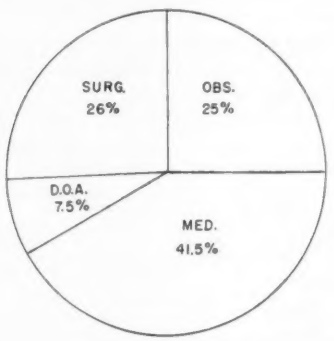

Figure 1. *Night Calls by Groups (D.O.A.=Dead on Arrival).*

years of age, 31 per cent being geriatric, and 8 per cent pediatric. But, if the obstetric cases are excluded, there were 69 females only, and the representation of age grouping becomes respectively 48 per cent, 42 per cent and 10 per cent.

Of the obstetric cases 42 were uncomplicated deliveries, and 2 were for examination only. Six cases presented the following complications: miscarriage, threatened miscarriage, stillbirth (2 cases), eclampsia and placenta praevia.

The small percentage of pediatric calls was unexpected. Of the 16 patients, 10 had upper respiratory infections, and the remainder a scattering of real or imagined difficulties. In 12 cases the call should have been made earlier or later, or was not justified.

Chief Complaints

The chief complaints are of interest. In 65 cases they were the obvious ones attendant on birth or death. With the exception of these cases the main reasons for requesting help in the other 135 cases are presented in Table 1. There were no other chief complaints representing more than 5 calls.

Table 1. *Chief Complaints.*

Reason for Call		No. of Cases
Pain (nontraumatic)		48
Abdominal	26	
Chest	11	
Head & ear	6	
Back	2	
Finger	1	
Leg	1	
Jaw	1	
Injury		23
Bleeding from bodily orifice		11
Dyspnea		7
Convulsion		6
Vomiting		5
Coma or stupor		5
Total		105

The importance of a complaint of chest or abdominal pain is indicated by the fact that, in the 11 cases of the former, 6 patients had coronary thrombosis, and of the 26 with abdominal pain, 12 were due to biliary-tract disease, generally with lithiasis, 2 to urolithiasis, 1 to mesenteric thrombosis and 1 to ruptured chocolate cyst.

Individual Diagnoses

An adequate diagnosis was made without difficulty in all but 2 of the 135 (other than obstetric or dead) patients at the bedside. The two missed diagnoses were hysteria (presenting as backache) and cholecystitis.

The diagnoses encountered 5 times or more from these complaints are shown in Table 2. There were 31 other conditions that involved all bodily systems without any pattern.

In general the chief complaint as described on the telephone made a presumptive diagnosis quite clear, and was a reliable clue. The degree of illness was, of course, largely exaggerated.

On the basis of bodily systems the medical conditions encountered were distributed as shown in Figure 2 (the dead being omitted). The surgical conditions were distributed as demonstrated in Figure 3.

Therapy

Definitive therapy was carried out (if needed) in 172 of the 185 living patients. Consultation was needed for treatment in 2 medical cases (these were diabetic ketosis and Stokes–Adams disease) and in 2 obstetric cases (eclampsia and placenta praevia). Consultations for surgical therapy were needed for fractures (3 cases), bleeding peptic ulcer (2 cases), epistaxis, ruptured chocolate cyst, cholecystitis, incisional abscess and urolithiasis.

Table 2. *Individual Diagnoses.*

Diagnosis	No. of Cases
Injury	23
Respiratory infections	15
Biliary-tract disease	11
Hysteria or neurosis	10
Cerebrovascular accident	8
Coronary occlusion	6
Gastroenteritis	5
Total	78

Excluding cases in which consultation was needed (and excluding obstetrics) the medications or treatments given are shown in Table 3. No other type of treatment was used more than twice.

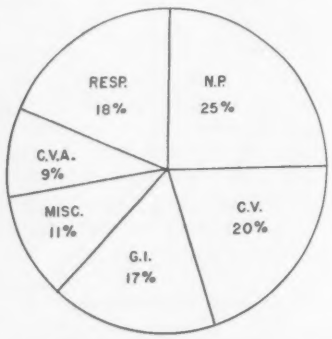

Figure 2. *Medical Conditions by Bodily Systems. N.P.=neuropsychiatric; C.V.=cardiovascular; G.I.=gastrointestinal; and C.V.A.=cerebrovascular accident.*

The original consideration was whether morphine (or sedation) alone was the usual treatment for most night calls; it was in 40 per cent. Antibiotics were the sole therapy in 6 per cent, and minor surgery accounted for 14 per cent. The three types of treatment used more than twice (including, when indicated, doing nothing) thus account for the handling of 68 per cent of all cases.

Discussion

The answer to the question how necessary night calls are varies with the time of day under consideration, and certainly with the point whether one has the symptoms or is being subject to call. Of the calls described above, 22 were clearly not necessary. In another 21 help should have been sought earlier or later, and 3 should have been handled by a dentist. Of the unnecessary calls minor respiratory infections, pains of neurotic origin and postseizure status were representative.

It is acknowledged that many cases caused a degree of worry and fear that, although found to be groundless by the physician, would, if he himself had been affected, have made outside help an obvious necessity.

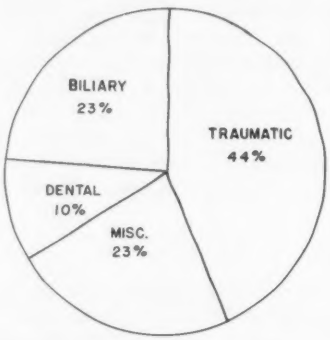

Figure 3. *Surgical Conditions by Types.*

But patients, ideally, could ease the annoyance of night calls in many cases by accepting telephone advice, being willing to consult the physician at the office (even to the alarming extreme of taking a child with a fever out of doors), seeking help earlier in the day or waiting the few hours until the working day begins. It seems reasonable that if a classic description of hives is given over the telephone, or if sunburn is given as the reason for the call, the patient's family should be willing to visit the physician's office for what palliatives he can offer.

Table 3. *Types of Treatment.*

Type of Treatment		No. of Cases
Sedation		69
Opiate	54	
Barbiturate	15	
Dressing or Suture		17
Antibiotic		11
Hemostatic		7
No treatment		13

Conclusions

Most night calls occurring in this type of practice are justified. If the measure of fright aroused by the

conditions encountered is used as a criterion, practically all such calls are valid, although one wishes that the critical degree of apprehension had been reached earlier in the day.

If the telephone rings between 11:30 p.m. and 8:00 a.m. the chances are even that the physician will encounter a parturient woman, a corpse or a sufferer from biliary-tract disease, respiratory infection or injury (that is, these cases collectively make up 50 per cent of all calls). If obstetric and the moribund are excluded from consideration the chances are even that the presenting complaint will be a respiratory infection, biliary disease, hysteria, cerebrovascular accident or injury. Except for this no generalization is possible, a wide variety of pathologic conditions presenting themselves.

Diagnosis will be uncomplicated.

For most nighttime complaints a few simple medications and facilities for minor traumatic surgery are sufficient. As a matter of fact, the only medications, besides sedatives and antibiotics, used in this series were quinidine, caffeine, aspirin, ergotamine tartrate, a hypotensive drug and an antihistaminic.

The night bell, by its timing alone, establishes no very definite diagnostic probabilities but does promise ease of diagnosis and therapy.

MEDICAL PROGRESS

HEMORRHAGIC STATES DURING PREGNANCY*

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ALTHOUGH uterine hemorrhage is one of the major complications of childbirth and a leading cause of maternal death, the underlying causes have been studied in detail only during the last few years, and knowledge of this subject is still fragmentary. Uterine hemorrhage is said to be due most often to atony, — that is, failure of the uterine musculature to contract immediately post partum, — which may result from local pathologic changes such as the presence of intramural fibromyomas or retained placental fragments, from overdistention of the uterus or from excessive anesthesia, shock or general debility; relatively fewer cases are attributed to vaginal or cervical lacerations. Bleeding from all these causes is usually controllable by local measures, and shock can be prevented or treated by such means as blood transfusion. It has become increasingly apparent, however, that when uterine bleeding is fatal, a disorder of blood coagulation is usually present. Alterations in the hemostatic mechanisms have now been described in a number of different pathologic states associated with pregnancy and the puerperium. An appreciation of these various disorders is important to institute rational therapy. However, it must be realized that knowledge of this subject is in its beginning stages. One should be cautious in accepting generalizations drawn from the few carefully observed cases that have been reported.

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BLOOD-CLOTTING MECHANISMS IN NORMAL PREGNANCY AND PARTURITION

The theories proposed to explain the coagulation of shed blood are myriad. The synthesis that follows is only one of many possible explanations of the clotting mechanism. Recent symposiums[1-3] provide more detailed information.

Clotting is produced by the conversion of a soluble protein, fibrinogen, into an insoluble protein, fibrin. This results from the action of an enzyme, thrombin, which is thought to be proteolytic. The conversion of fibrinogen to fibrin is accelerated by calcium ions in the concentration present in shed blood. There is also evidence that a factor in normal plasma may accelerate this process.

Thrombin presumably does not exist as such in any appreciable amount in the normal circulating blood, but is present as a precursor, prothrombin. A major portion of current debate concerning blood clotting centers around the means by which the prothrombin of the circulating blood is changed to thrombin when the blood is shed. This change is thought to take place through the action of a group of substances that generically may be called thromboplastin. Thromboplastin is found in animal tissues, including the placenta, and in amniotic fluid. Thromboplastic properties also appear in shed blood uncontaminated with other tissues. The platelets probably disrupt early in the clotting process, and classically have been thought to liberate thromboplastin, thus initiating clotting. However, considerable evidence has accumulated that when blood is shed and comes in contact with a wettable surface, thromboplastinlike activity appears in the plasma itself, independent of any cellular elements. A number of factors may contribute to this

activity — notably, antihemophilic factor (or thromboplastinogen), plasma thromboplastin component (or Christmas factor), plasma thromboplastin antecedent, a fourth thromboplastin component and Hageman factor, a newly described, stable globulin fraction of plasma. Under ordinary conditions the conversion of prothrombin to thrombin also requires the presence of calcium ions, and is accelerated by at least two other factors — namely, accelerin (serum accelerator globulin, Factor VI) and convertin (serum prothrombin conversion accelerator). The mechanisms by which accelerin becomes activated from its precursor, proaccelerin (Factor V, plasma accelerator globulin, labile factor), and then achieves its accelerating effect are not yet clear. There is some evidence that convertin (or its precursor, proconvertin, co-thromboplastin or Factor VII) reacts with thromboplastin and calcium ions to form an "activated" thromboplastin, which in turn converts prothrombin to thrombin.

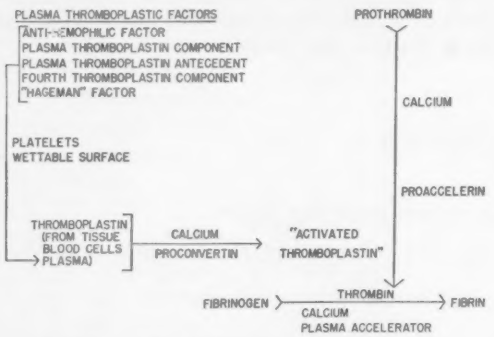

FIGURE 1. *Outline of the Clotting Mechanism.*
Some of the synonyms for the various factors are listed in the text. There is considerable evidence that proconvertin and proaccelerin must be converted respectively to convertin and accelerin to be effective. Various naturally occurring inhibitors of clotting have been omitted from the diagram.

The role of platelets in the clotting process is much less clear than it seemed some years ago. Platelets appear to be necessary for the optimal conversion of prothrombin to thrombin in ordinary clotting. They are probably needed for the rapid development of plasma thromboplastic activity, are essential for clot retraction and appear to possess vasoconstrictor activity. The nature of the surface with which shed blood comes in contact is also of great importance in determining the rapidity with which it will clot. Such nonwettable surfaces as vaseline, paraffin and silicone appear to delay the clotting process, whereas glass and metallic surfaces accelerate it, presumably by increasing the rate at which thromboplastic activity appears in the shed blood. These views are summarized in Figure 1.

Human plasma also contains a potent proteolytic enzyme or enzymes capable of digesting fibrinogen, fibrin, proaccelerin, prothrombin and immune complement, as well as casein, gelatin, denatured hemoglobin and several synthetic amino acid esters. This enzyme (plasmin, fibrinolysin) is ordinarily in an inactive form (plasminogen, profibrinolysin), but may be activated spontaneously in shed blood or by the addition of chloroform, tissue particles or streptokinase, a principle found in filtrates of cultures of certain beta-hemolytic streptococci. There is evidence that, under some conditions, the clotting process may potentiate the activation of plasminogen. It has been reported that exercise, shock, the injection of epinephrine and electroconvulsive therapy, as well as a variety of pathologic states, may result in increased activation of plasminogen, as detected in vitro. Rarely, such activation may occur in vivo to a degree sufficient to cause a hemorrhagic state. It is noteworthy that plasma not only is potentially fibrinolytic but also has strong plasmin-inhibiting activity, an effect that appears to be due to the action of several different substances.

Clotting Changes

There have been many studies of the clotting mechanism during normal pregnancy. At term, the clotting time[4-6] and bleeding time[5] are usually normal. It has been known for some time that the concentrations of prothrombin and fibrinogen usually increase during pregnancy. Plass, in 1926, determined that the fibrinogen rose from an average of about 300 mg. per 100 cc. in nonpregnant women to about 370 mg. in the thirteenth to the sixteenth week and an average of 440 mg. in the thirty-seventh week and thereafter; these data are typical of others that have been published. The increase in the concentration of fibrinogen is apparently important in producing the rapid erythrocyte sedimentation rate characteristic of pregnancy. Recently, it has been demonstrated that the proconvertin activity of plasma increases during pregnancy.[7]

The concentration of platelets in the circulating blood has been reported to be normal, decreased or elevated in normal pregnant women. We have been unable to demonstrate any significant changes in the platelet count of parturient women.[6] The thrombin time — that is, the time required for the clotting of a mixture of oxalated plasma and bovine thrombin — is normal in the third trimester of pregnancy[8] and at the time of parturition.[6] Finally, at the onset of labor there is no evidence of abnormal plasma fibrinolytic activity; plasma clots lyse in the same time as the clots of nonpregnant subjects.[5,6]

Few alterations in the clotting mechanism have been detected during the course of normal labor and in the immediate post-partum period. The clotting time, the concentration of prothrombin and the thrombin time remain unchanged.[5,6] Slight but inconsistent changes in the concentrations of fibrinogen and platelets have been observed.[6] However, after delivery there is an increase in the plasma fibrinolytic

activity.[5,6] The time that elapses until clotted plasma dissolves shortens from three or more days ante partum to a minimum of less than twenty-four hours, two to four hours post partum. By the next day clot lysis has usually returned to normal. The cause of this rapid fibrinolysis is not known, nor is its significance in the bodily economy. The rapid lysis does not appear to result from a decrease in the inhibitory activity of the plasma against plasmin or from a change in the amount of available substrate.[6]

Control of Uterine Bleeding after Delivery

Relatively little is understood concerning the control of bleeding from the placental site after the expulsion of the placenta. Immediately after the delivery of the child, the uterus contracts, the contracting myometrium constricts the intrauterine blood vessels, and the flow of blood from the raw placental bed is checked. Whether or not blood coagulation plays a significant part in the immediate control of hemorrhage is not clear. Greenberg[9] observed that the blood expelled from the uterus after the separation of the placenta was usually incoagulable. Barnes[10] demonstrated that this blood did not clot when thrombin was added, indicating that it was devoid of fibrinogen. However, the addition of fibrinogen alone did not result in clotting. Both fibrinogen and thromboplastin had to be added to post-partum uterine blood to induce coagulation. The clot that then formed did not undergo lysis. Barnes further demonstrated that the continued administration to the mother of Dicumarol or heparin in therapeutic doses did not increase blood loss from the uterus in the puerperium. Moreover, patients with thrombocytopenic purpura may be delivered without any unusual blood loss, as reported by Epstein et al.,[11] Peterson and Larson[12] and others, and childbirth in a female patient with true hemophilia was not attended by *immediate* uterine hemorrhage.[13] Barnes[10] believed that the ability of the blood to clot plays little part in the early control of post-partum uterine bleeding and that hemostasis is effected primarily by adequate myometrial contraction. However, it should be pointed out that a conclusive answer to the role of the clotting mechanism is not at hand. It is possible that the blood of patients with severe coagulative defects will clot on contact with the thromboplastic raw tissues at the site of implantation of the placenta. Only in a patient with afibrinogenemia would one expect no clotting at all under these circumstances. The data reported by Greenberg[9] and Barnes[10] may well be explained by the formation of clots within uterine vessels and at the placental site. The incoagulable uterine blood would then actually be a mixture of extruded cells and serum. Only further studies will clarify this subject.

Hemorrhagic States Associated with Pregnancy

Under a number of conditions more or less transitory abnormalities in the clotting mechanism occurring at or near the time of parturition may be responsible for uterine or generalized bleeding. These syndromes include premature separation of the placenta, amniotic-fluid embolism, the presence in the uterus of a dead fetus and eclampsia or severe pre-eclampsia. A generalized bleeding tendency may also occur early in pregnancy, as a sequel to criminal abortion. The exact mechanisms ultimately responsible for the bleeding tendency in each of these states is unknown.

Experimental Intravascular Defibrination

Several investigators have proposed that the bleeding associated with premature separation of the placenta, amniotic-fluid embolism or the intrauterine retention of a dead fetus may be secondary to a depletion in the amount of circulating fibrinogen. In turn, this may be the result of the coagulation of fibrinogen within the maternal blood vessels. In experiments upon animals, Woolridge, in 1886, observed that the slow intravenous infusion of tissue thromboplastin rendered the blood incoagulable. Mills, in 1921, showed that this was accompanied by a decrease in the concentration of fibrinogen in the circulating blood. The decrease in fibrinogen is presumably the result of intravascular clotting; Obato, in 1919, and others[14,15] have demonstrated thrombi microscopically in the smaller blood vessels. If the injection of thromboplastin is rapid the animal may die; at autopsy, clots are found in the lumens of the pulmonary arteries, the inferior vena cava and the portal vessels. If the injection is gradual, however, complete defibrination may take place without obvious harm to the animal. Several hours after the infusion is completed, the concentration of fibrinogen in the circulating blood begins to rise, and within twenty-four hours the level may actually be higher than before the infusion. Other alterations in the clotting mechanism may be noted during the infusion of thromboplastic material. The clotting time gradually lengthens until the blood becomes incoagulable; there may be thrombocytopenia, and the clotting time of a mixture of oxalated plasma and thrombin may be prolonged.[16,17] Under certain conditions excessive plasma fibrinolytic activity may also be demonstrated, but this is an inconstant finding. Similar changes have been described after the intravenous injection of other clot-promoting agents. The striking resemblance between these events and those observed in some of the patients with hemorrhagic disorders of parturition will be apparent. It is therefore of interest that in some of the experimental studies that have been reported placental tissues and amniotic fluid have been used as the thromboplastic materials.

Detection of Hypofibrinogenemia and Afibrinogenemia

The terms hypofibrinogenemia and afibrinogenemia have been used loosely in the recent literature. The latter should be reserved for a condition in which no fibrinogen is detectable. When the concentration

of fibrinogen falls to about 100 mg. per 100 cc. of plasma or less, generalized hemorrhagic symptoms such as epistaxes, hematuria, melena, cutaneous ecchymoses after trivial injuries, gingival bleeding and bleeding at the sites of venepunctures or parenteral injections may appear. Post partum, uterine bleeding may be prolonged or excessive. It must be remembered, however, that normally the first blood that flows from the uterus after delivery clots poorly if at all[9,10] so that *failure of uterine blood to clot is not of itself evidence that hypofibrinogenemia is present.*

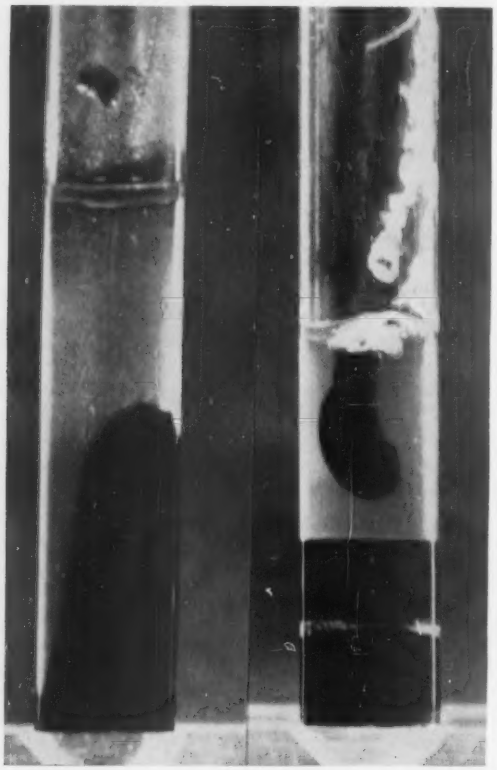

FIGURE 2. *Clot Retraction As a Clue to Hypofibrinogenemia.*

Blood from a normal person (left) and from a patient with hypofibrinogenemia (right) was allowed to clot in Pyrex tubes. As can be seen, most of the red blood cells were extruded from the smaller clot.

Hypofibrinogenemia or afibrinogenemia can be detected by observation of the effect of bovine thrombin on the patient's blood or by actual determination of the concentration of fibrinogen in the patient's plasma. Despite a number of reports to the contrary, the clotting time of whole blood is of little or no value except if the blood is incoagulable. The clotting time may be prolonged despite the presence of normal amounts of fibrinogen, and may be normal even though there is hypofibrinogenemia. However, the gross appearance of the patient's clotted blood may be of some help.

The operating room should be provided with scrupulously clean Pyrex-glass test tubes, either 10 by 75 or 13 by 100 mm. in size. Some of the tubes should be scored at the 1-cc. mark. The scored tubes should contain 0.1 cc. of topical thrombin solution (1000 National Institutes of Health units per cubic centimeter). This is the same topical thrombin preparation found in most surgeries and emergency wards. These thrombin tubes should be stored in a deep freeze. The deep freeze used in many hospitals for the storage of placentas is a convenient place for this purpose. In addition glass tubes or bottles containing dry oxalate salts should be immediately available. The ordinary ammonium oxalate and potassium oxalate blood-count bottle is suitable.

When hypofibrinogenemia is suspected, about 10 cc. of venous blood should be drawn immediately, preferably through an 18-gauge needle. The needle should be removed from the syringe, a tube containing thrombin should be filled to the 1-cc. mark, 5 cc. of blood should be added to the oxalate bottle and mixed thoroughly, and about 3 cc. of blood should be transferred to an empty Pyrex tube. Failure of the blood to form a clot in the tube containing thrombin is indicative of afibrinogenemia. If hypofibrinogenemia is present, a clot may form that is either small in appearance or shrivels after a few minutes to a small size either spontaneously or upon gentle tapping of the tube. A firm clot that is of good size suggests that a normal amount of fibrinogen is present in the tube. Obviously, it is of great importance for the physician to have personal experience with the appearance of normal thrombin clots. This test, advocated for the present purposes by Page,[18] gives an almost immediate answer, since the clotting time of a mixture of normal blood and thrombin is only a few seconds. The presence of afibrinogenemia will also be indicated by failure of the 3 cc. of blood in the plain Pyrex tube to clot. If hypofibrinogenemia is present the blood in this tube may clot in a normal time, but the coagulum may look small and flabby. If clotting does take place in either the thrombin or the plain glass tubes the clots should be observed at frequent intervals for fragmentation or lysis. A sensitive indicator of hypofibrinogenemia is the separation of red cells from the clot (Fig. 2), as described by Weiner, Reid and Roby.[19] If the amount of fibrin formed is small, almost all the red cells are extruded as the clot retracts. A similar picture is seen during the lysis of a clot, and may be a source of confusion.

If there is any question concerning the presence of hypofibrinogenemia, a quantitative determination can be made on the plasma of the oxalated sample. This procedure, however, takes a little more than an hour — time that may not be available.

The distinction between hypofibrinogenemia and

fibrinolysis is not yet of therapeutic importance. However, inadequate appreciation of the difficulties in making this distinction have led to a number of incorrect inferences concerning the pathogenesis of hemorrhagic states. In severe hypofibrinogenemia the clot often retracts quickly to a tiny nubbin from which the cells are extruded. Investigators have repeatedly ascribed this rapid clot retraction to fibrinolysis. This conclusion is probably not correct unless the clot disappears completely. The converse inference — that total dissolution of a clot is diagnostic of hypofibrinogenemia — has also been drawn and is similarly unjustified.

Fibrinolysis can be detected most readily by observation of the clot formed by addition of calcium[20] or thrombin[6] to oxalated plasma. One may measure the amount of fibrin digested within a given time, but this is a much more cumbersome procedure than observation of the clot-lysis time — that is, the time elapsing until a clot dissolves completely. In most normal persons the clot-lysis time at 37°C. is longer than two days. However, much more rapid clot lysis occurs in many pathologic states unassociated with hypofibrinogenemia or hemorrhagic symptoms. It is likely that fibrinolysis is of clinical significance in hemorrhagic states only when the clot-lysis time is a matter of an hour or two or less. When hypofibrinogenemia or afibrinogenemia is present, it is necessary to mix the patient's plasma with human or bovine fibrinogen to test for fibrinolysis. Needless to say, suitable control experiments must be performed before hypofibrinogenemia or hemorrhagic symptoms are ascribed to fibrinolysis.

Premature Separation of the Placenta

Probably the most frequent cause of excessive blood loss in pregnancy is premature separation of the placenta. Premature separation is a common complication of pregnancy; in different series the frequency varies from 1:85 to 1:250 deliveries. In a small proportion of these cases the uterine bleeding that results is serious and may even be fatal. DeLee, in 1901, observed that the uterine bleeding in a patient with premature separation was associated with generalized bleeding phenomena. However, the patient described had a history of hemorrhagic difficulties long antedating the premature separation. Willson, in 1922, reviewed a number of cases associated with bleeding phenomena and attributed these to the liberation of a hemorrhagic toxin by the placenta. The true nature of the disorder was elucidated in 1936 by Dieckmann, who demonstrated that a coagulation defect associated with severe hypofibrinogenemia was present in several cases of premature separation of the placenta. This observation has been amply confirmed. In some cases the hypofibrinogenemia has been accompanied by thrombocytopenia,[21-24] hypoprothrombinemia[22,24-26] and a deficiency in the concentration of proaccelerin in the plasma.[22,25,26]

The pathogenesis of hypofibrinogenemia in association with premature separation of the placenta is a matter of conjecture. Dieckmann suggested that the fibrinogen was lost through hemorrhage and utilized at the site of placental separation. Moloney, Egan and Gorman,[27] on the other hand, believed that the fibrinogen had been destroyed, presumably by plasmin, the fibrinolytic enzyme or enzymes of plasma that are active at the pH of the blood. Increased fibrinolytic activity has been observed under these conditions by a number of investigators.[19,22,28,29] However, it seems unlikely that fibrinolysis is the primary cause of the clotting defect in premature separation of the placenta, for in a number of such cases with hypofibrinogenemia it has not been possible to demonstrate abnormal fibrinolytic activity.[23-25]

In a 24-year-old Negress studied at University Hospitals of Cleveland, premature separation of the placenta occurred during the 6th month of pregnancy in association with preeclampsia. The patient noted profuse gingival bleeding on the morning of admission. All studies of the clotting mechanism were negative except that the concentration of fibrinogen in the plasma was 131 mg. per 100 cc. with the use of a method in which the concentration in 36 normal nonpregnant women ranged from 164 to 485 mg. per 100 cc. Clots of the patient's whole blood and cell-free plasma, obtained without the addition of an anticoagulant, did not dissolve during a period of 2 weeks when incubated at 37°C. Moreover, no abnormality was observed in the inhibitory activity of the plasma against bovine plasmin. She was delivered without difficulty, and 5 days later the plasma fibrinogen concentration was 574 mg. per 100 cc.

A more striking case was that of a 26-year-old primipara observed at Euclid-Glenville Hospital. Four hours after the onset of labor she had a sudden severe uterine hemorrhage associated with symptoms of premature separation of the placenta. About 90 minutes later she had hemoptysis, and venous blood was found to be incoagulable when mixed with thrombin solution. After the administration of 1500 cc. of citrated blood and 4 gm. of human fibrinogen the concentration of fibrinogen in the patient's plasma was 178 mg. per 100 cc. Despite the afibrinogenemia before transfusion it was not possible to demonstrate that the blood had abnormal fibrinolytic activity at any time. Concomitant with the total afibrinogenemia the prothrombic activity of the plasma was only 34 per cent of normal, with the use of a method in which proaccelerin, proconvertin and fibrinogen were provided in excess. Platelet counts were not performed, but no clot retraction was noted in the blood drawn just after the injection of fibrinogen. The thrombin time was greatly prolonged. The abnormal clot retraction and thrombin time may have been related to the fact that this patient had severe toxemia of pregnancy. About 5 minutes after the injections of blood and fibrinogen had been completed, she had an eclamptogenic convulsion. Twenty minutes later, a recently dead fetus was delivered by cesarean section. The patient's subsequent course was uneventful.

A more probable explanation for the hypofibrinogenemia in premature separation of the placenta is that it results from intravascular coagulation of the maternal blood. If thromboplastic material gained access to the maternal blood stream it might result in intravascular fibrin formation in the manner described. Obato, in 1919, and subsequent workers[30,31] have shown that placental tissue is highly thromboplastic, and defibrination can be produced in laboratory animals by the intravenous injection of placental tissue. For this reason it is tempting to assume that

the hypofibrinogenemia seen in premature separation of the placenta is due to the thromboplastic effects of placental tissue, a hypothesis advanced by Schneider,[29] Page,[25] Weiner and his associates[32] and others. Such intravascular clotting would account for the depression of other components of the clotting system as well. The tissues of patients who have died shortly after premature separation contain intravascular fibrin deposits throughout the body, particularly in the lungs, kidneys and liver, supporting this point of view.[29,33] The excessive fibrinolytic activity described in some cases may have resulted from the concomitant shock,[34] perhaps combined with the normal increase in plasma fibrinolytic activity associated with parturition.[5,6] The low concentration of the substrate, fibrinogen, would tend to exaggerate the effects of any increased fibrinolytic activity.

It should be emphasized that the view that the decrease in fibrinogen is the result of intravascular defibrination is conjecture. It is possible, for example, that the solubility of the fibrinogen is reduced and that this protein is then precipitated in the small blood vessels as an insoluble substance that is not, however, true fibrin. Recent studies by Thomas et al.[35] suggest that such an alteration may occur under certain experimental conditions.

Treatment of a patient with the hemorrhagic diathesis associated with premature separation of the placenta consists of three parts. In the first place the patient should be treated promptly for the effects of blood loss and shock in the same manner as any other patient. Secondly, she should be given an intravenous injection of 4 gm. of purified human fibrinogen, a practice introduced by Moloney and his associates.[27] If fibrinogen is not available repeated blood transfusions will be needed to raise the concentration of fibrinogen in the patient's plasma. On the average 1 liter of blood contains 1.5 gm. of fibrinogen. If the hypofibrinogenemia is not corrected by this procedure, repeated injections of fibrinogen may be necessary. For example, Drs. John Harris and Robert Griggs, at Cleveland City Hospitals, recently studied a patient in whom hemostasis was achieved only after the injection of 16 gm. of fibrinogen and the transfusion of 11 units of blood. Thirdly, measures should be taken to empty the uterus. Weiner, Reid and Roby[32] suggest that labor be induced by rupture of the fetal membranes, and only if effective labor does not ensue in four to twelve hours should cesarean section be performed. In our experience, if the cervix is not long and closed and amniotomy can be performed readily, this procedure should be carried out. However, if labor does not follow promptly, if it is difficult to keep the patient out of shock or if laboratory studies show that fibrinogen depletion is continuing at a rapid rate, it is probably in the best interest of the patient to empty the uterus promptly by cesarean section. It should be pointed out that without the injection of purified fibrinogen, most patients with the hemorrhagic diathesis associated with premature separation can be treated successfully without resort to surgical procedures.

Death may occur even though the uterus is emptied and the patient has been treated with fibrinogen. The defects in the hemostatic mechanism may be corrected, and the patient may appear to recover only to go into renal failure,[36] whose outcome may be fatal.

A 39-year-old Negress had uterine bleeding during the 39th week of her 3d pregnancy. About 3 hours later the fetal heart beat could no longer be heard; 2 hours thereafter the membranes ruptured, and about 1 hour later, under spinal anesthesia, a stillborn fetus was delivered. Concomitant with the administration of the anesthesia the blood pressure dropped, and the patient went into shock. Post partum there was brisk uterine hemorrhage, as well as bleeding at the sites of venepunctures. Because of the collapsed state of the veins it was not possible to do adequate hematologic studies. Four grams of human fibrinogen was given intravenously, the only obvious result of which was the appearance of clots in the blood flowing from the uterus. Despite numerous transfusions and supportive therapy, the patient died 7 hours post partum. The only pathologic finding was a hemorrhagic area along 1 edge of the placenta suggestive of premature separation. No amniotic-fluid emboli were found.

(To be concluded)

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MEDICAL INTELLIGENCE

PROSTHESES AFTER AMPUTATION FOR MALIGNANT LESIONS

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BOSTON

THE cost of an artificial limb, along with the expenses incident to a preliminary examination, x-ray studies, physiotherapy and, finally, training in the use of the limb, is a sizeable sum. As a result the question frequently arises whether it is medically advisable or economically sound to expend such a sum of money in behalf of a patient who has undergone an amputation because of a malignant process occurring in an extremity.

It is a general impression among doctors that the prognosis for life in such patients is poor. However, because these cases are not very numerous, few persons or agencies have been able to assemble a sufficient number to give a satisfactory answer to the problem. This report represents the experiences of 17 vocational rehabilitation agencies throughout this country. Although the number of cases is not large certain conclusions seem warranted.

A few agencies have refused to purchase prostheses for applicants with cancer of the extremity because it was considered wiser to expend the available money on behalf of a client whose life expectancy was more certain. In some cases a "waiting period" was required. This ranged in duration from a few months to a few years. It was the intent of such a plan to weed out applicants in whom evidence of spread of the cancer might develop shortly after operation. In general it can be said that there is considerable indecision concerning the matter.

A poll of the rehabilitation agencies brought reports of 84 cases. A total of 55 sufficiently complete cases has been assembled. It has not been possible to verify the diagnoses, but they are said to have been taken from the hospital records of the applicants. All information concerning the progress of the patients was taken from the records of the rehabilitation counselors, persons who are specially trained in such work. The cases, in all of which prosthetic devices were furnished, are listed in Table 1.

TABLE 1. *Data in 55 Cases after Amputation.*

DIAGNOSIS	NO. OF CASES	NO. OF DEATHS
Osteogenic sarcoma	29	11
Fibrosarcoma	9	3
Squamous-cell carcinoma	5	1
Synovioma	4	3
Neurofibroma	2	0
Neurogenic sarcoma	2	1
Chondrosarcoma	1	1
Spindle-cell sarcoma	1	1
Hemangioendothelioblastoma	1	1
Osteochondromyxosarcoma	1	0
Totals	55	22

TABLE 2. *Survival after Amputation in Patients Who Died.*

INTERVAL BETWEEN AMPUTATION & DEATH	NO. OF PATIENTS
yr.	
1	4
2	5
3-5	9
6 or more	4
Total	22

The majority of these patients were males, and, although they ranged from ten to fifty-five years of

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age, many were in the younger adult age groups. These figures are of no significance.

From Table 1 it is seen that 40 per cent of those given prostheses subsequently died. An analysis of those deaths is recorded in Table 2.

TABLE 3. *Periods of Survival in Living Patients.*

SURVIVAL AFTER AMPUTATION	NO. OF PATIENTS
yr.	
2	9
3-5	7
6-10	10
11 or more	7
Total	33

There were 33 patients in this series who survived. The periods of survival are listed in Table 3.

By combining part of Table 2 with all of Table 3 it becomes evident that 51 patients, representing 93 per cent of the total given prostheses, survived for two years or more. In a review of the available data no evidence was found that the provision of a prosthesis immediately on surgical recovery had any adverse effect on the prognosis, nor was it possible to demonstrate any greater survival rate among patients whose prostheses were not supplied until long after the amputation (Table 4).

TABLE 4. *Survival Periods in Relation to Interval before Prostheses Were Supplied.*

INTERVAL AFTER AMPUTATION	NO. OF APPLIANCES PURCHASED	NO. OF SURVIVORS	PERCENTAGE OF GROUP
mo.			
2	1	1	100
3	2	2	100
4	2	2	100
5-6	18	11	61
7-12	14	5	36
13-24	10	6	60
25 or more	8	6	75

It was not possible to demonstrate any statistically valid correlation between the age of the patient and his period of survival although the mortality in the younger and older age groups appeared higher.

The 29 patients with bone sarcoma were studied in more detail. The rate of survival and other conclusions were identical with those of the group as a whole.

SUMMARY AND CONCLUSIONS

In this series the majority (93 per cent) of patients with cancer of an extremity survived two years or longer after amputation. Almost all who survived became engaged in gainful employment. The types of employment varied widely. On the assumption that the average weekly wage of those who survived longer than a year was a low of $35 the total earnings of the first year for the group would be $92,820. Taxes (estimated as 10 per cent of gross income) paid by the group surviving at least two years would be $18,564, or about $2,000 more than the total expenditure of $16,500 for the 55 prosthetic devices (at an average cost of $300 each). The aggregate taxes paid in ten years, adjusted for those who did not survive, would total $73,968. This indicates that it is financially sound to purchase such prostheses. The independence and psychologic lift given to such patients cannot be measured in dollars but is certainly worth a great amount.

No evidence has been found that a waiting period before the purchase of the prosthesis is of any value in increasing the percentage of favorable cases. Therefore, it seems reasonable to proceed with the purchase of a prosthesis whenever the medical and surgical indications warrant it.

There is no evidence that the wearing of a prosthesis has contributed in any way to an increased morbidity and mortality.

We are indebted to the divisions of vocational rehabilitation in Arkansas, Florida, Maine, Maryland, Minnesota, Mississippi, Montana, North Carolina, Ohio, Pennsylvania, Rhode Island, Utah, Vermont, Washington, Wisconsin, the Territory of Hawaii and the Commonwealth of Puerto Rico for co-operation in providing the data on which this study was based.

WILLIAM JAMES ON PHANTOM LIMBS

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BOSTON

IN 1887 William James reported to the American Society for Psychial Research his study of 185 persons after amputations, his interest in this subject being no doubt stimulated by the fact that his father had had a midthigh amputation. It may seem strange today that a professor of philosophy should probe into so unphilosophical a matter as phantom pain, but it is pertinent to recall that James was an assistant professor of physiology before he began his pursuit of philosophy.

James, in this report, noted that three fourths of the persons studied had sensations referred to the lost part, some positively, some dubiously, depending on their state of consciousness. Some ceased to feel the limb immediately after its severance; in others the consciousness of it lasted for weeks, months or years. In this respect he revealed that his father, Henry James, who had a midthigh amputation at thirteen, after he was seventy "affirmed his feeling of the lost

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foot to be every whit as distinct as his feeling of the foot which remained."

According to James, consciousness of the lost limbs varies from acute pain, pricking, itching, burning, cramps, uneasiness, numbness in toes, heel or other places, to feelings that are hardly perceptible. He found that feelings are not due to the condition of the stump, for feeling existed in both healthy and painful stumps.

The hand and foot are usually the only lost parts very distinctly felt, the intervening tracts seeming to disappear although some patients do feel the knee or the calf. James also reported that it is a common experience during the first week after amputation for the patient to forget that his leg is gone and to walk off the bed, only to fall.

Generally, the position of the lost leg follows that of the stump and artificial leg. If one is flexed the other seems flexed. In some cases the lost leg maintains a more or less fixed position of its own that is independent of the artificial leg. One person with such symptoms told James that he felt as if he had three legs in all, and sometimes became confused in going downstairs, between the artificial leg, which he put forward, and the imaginary leg, which he bent backward. Another patient felt constantly a blister on his heel, which had been there at the time of his accident.

About 100 patients who felt their feet affirmed that they could "work" or "wiggle" their toes at will. About 50 denied any such power. This, again, seems unrelated to the condition of the stump or the site of amputation.

"The popular mind wonders how the lost feet can still be felt. For us, the cases for wonder are those in which the lost feet are not felt." Some patients and their families are still quite disturbed and puzzled by phantom feelings. One man said recently that he thought these phantom feelings meant that he was going crazy, and his wife later told me that she was sure he was. Both were considerably relieved and reassured when they were told that such feelings are quite normal. One may properly ask if more attention should not be given to the orientation of these patients regarding phantom feelings.

James explained lack of feeling in terms of three possible conditions:

> Degeneration of perceptive nerve centers.
>
> Nerve ends so softly embedded in stumps as to carry up no impression to the brain, or none strong enough to be noticeable.
>
> The tendency to overlook feeling since it is of no practical use to consciousness. "It is a superfluous item in our conscious baggage."

A lost foot, in some patients, can be made to feel warm or cold by warming or cooling of the stump. A draught of air on the stump produces the feeling of a draught on the foot.

James was puzzled by the fact that in 50 cases there was no feeling of change in position of the imaginary extremity even when the stump muscles contracted violently. "This is not due to the fact that the amputation is made above the origin of the hand-or-foot moving muscles, for there are eleven cases where these muscles remain and contract, but yet no sense of movement exists."

He includes a final note for those especially interested in "psychic research." He reports little evidence to confirm the belief that when a cut-off limb is maltreated in any way, the patient, no matter where he is, will feel the injury. (This superstition is still alive, for several patients have recounted to me their intense pain at the time their cut-off limbs were supposed to have been destroyed.)

If present readers find it curious that James should include a reference to so extravagant a notion, they may be interested to know that, at the time he wrote, a committee on apparitions and haunted houses, with the philosopher Josiah Royce as chairman, was functioning as part of the American Society for Psychial Research. In passing it may be noted that among the members of this Society, besides Royce and James, were Morton Prince, G. Stanley Hall, Benjamin Pierce and many other notables.

Finally, it must be recorded that James never lost his interest in psychic research, much to the embarrassment of his colleagues at Harvard. If anyone is led to conclude that, because of his penchant for psychic research, James was tender minded rather than tough minded, the following quotation written many years before the atomic bomb may be of interest:

> [Man's] practical control of nature [he pointed out], accelerated so that no one can trace the limit; one may even fear that the being of man may be crushed by his own powers, that his fixed nature as an organism may not prove adequate to stand the strain of the ever increasingly tremendous functions, almost divine creative functions, which his intellect will more and more enable him to wield. He may drown in his wealth like a child in a bath-tub, who has turned on the water and who cannot turn it off.

CASE RECORDS
OF THE
MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 41281

PRESENTATION OF CASE

A thirty-year-old woman entered the hospital because of headaches, anorexia, nausea and vomiting.

Fifteen years before admission she had migratory polyarthritis. A diagnosis of rheumatoid arthritis was made, and she was hospitalized for six months and treated with gold injections. Some time after discharge when ankle, leg and periorbital edema developed she was told by her physician that she had kidney disease. The edema subsequently disappeared. Ten years before entry she was readmitted for a flare-up of the arthritis. Gold therapy was not used this time because it was thought that she was sensitive to it. During this hospitalization she had a reaction to a sulfonamide consisting of dermatitis and fever. Eight years before entry she was again admitted for study because of albuminuria. At this time she had some nausea and intermittent ankle and periorbital edema. About six years later she was refused insurance because of albuminuria. Morning headaches appeared about that time and subsequently increased in frequency and severity. Six months before entry she entered the same hospital for the fourth time because of edema, nausea, vomiting and headaches. Intravenous pyelograms showed shrunken kidneys, which excreted some dye. Urine cultures then and subsequently were negative. After discharge the headaches became increasingly more severe. They lasted a few hours to a few days, occurred at any time of the day or night, were usually retro-orbital and were occasionally preceded by flashing of lights. She was seen by an otolaryngologist and an ophthalmologist, who found no evidence of sinusitis or eye disease. One month before admission she made a long bus trip, which resulted in exacerbation of the symptoms of nausea, vomiting and headache. Shortly after she awoke on the day before admission one of the severe headaches began, this time on the left side. Empirin and codeine gave no relief. Later in the day she vomited; she was anorectic all day.

There was no history of rheumatic fever or rheumatic heart disease. The family history revealed that a grandmother had hypertension and heart trouble; her mother may have had hypertension; and a grandfather had bronchial asthma.

The patient was a rather poorly nourished young woman. The lungs were clear. The heart was not enlarged. A Grade 2 soft systolic murmur was heard at the apex and along the left sternal border. The aortic second sound was snapping and was louder than the pulmonic. There was questionable periorbital and finger edema but no ankle edema. The fundi showed a widened vascular light reflex but were without hemorrhages or exudates; the disks were not remarkable.

The temperature was 97.6°F., the pulse 92, and the respirations 20. The blood pressure was 160 systolic, 100 diastolic.

Urinalysis revealed a specific gravity of 1.008, a + test for albumin and 30 red cells and 2 white cells per high-power field in the sediment; culture was negative. Examination of the blood showed a hemoglobin of 7.8 gm. per 100 cc. and a white-cell count of 7700, with 65 per cent neutrophils, 26 per cent lymphocytes, 7 per cent monocytes and 1 per cent eosinophils. The nonprotein nitrogen was 76 mg., the albumin 4.0 gm., the globulin 1.3 gm., the phosphorus 7.5 mg., and the calcium 7.3 mg. per 100 cc.; the carbon dioxide was 17 milliequiv., the potassium 4.8 milliequiv., and the sodium 132 milliequiv. per liter.

The patient was placed on a diet containing 40 gm. of protein and 500 mg. of sodium. Two transfusions were given during the first week. Chlorpromazine (Thorazine), 150 to 175 mg. per day, was administered. Other therapy included codeine, barbiturates, aspirin, Amphojel and Mercuhydrin. Headache and nausea persisted. Later, after liberalization of sodium intake and forcing of fluid up to 3 liters a day, edema increased. Testosterone, 25 mg. a day, was administered for a period of six days, and daily penicillin was begun. On the twenty-fifth hospital day, she had an episode of cough, dyspnea and frothy sputum, accompanied by bilateral pulmonary rales. At this time there was gross edema. The muscles were markedly tender. There were dullness and decreased breath sounds at the right-lung base. Two or three flame-shaped hemorrhages were seen in the eye grounds, and the disk margins were hazy. The blood pressure was 190 systolic, 120 diastolic. The urine had a specific gravity of 1.009 and a pH of 6, and gave a +++ test for albumin; the sediment contained over 100 red cells, 2 or 3 white cells and rare granular and cellular casts per high-power field. Urinary protein excretion was 2.82 gm.; the sodium was 45 milliequiv. per liter per twenty-four hours. Creatinine clearance was 4.3 liters per twenty-four

hours. The hemoglobin was 9.2 gm. per 100 cc., and an eosinophil count 264 per cubic millimeter. The serum cholesterol was 212 mg. per 100 cc. An LE preparation was negative. The fluid intake was now restricted to 1200 cc. per twenty-four hours, and digitalization was begun. The patient became dyspneic, and dullness and rales appeared at the lung base. An inconstant diastolic gallop and apical friction rub were heard. An x-ray film of the chest showed moderate cardiac enlargement, pulmonary congestion and free fluid in both pleural cavities. Apresoline, 25 mg. every four to six hours, and cortisone, 200 mg. per twenty-four hours, were begun. The cortisone was discontinued after six days. Two days later tenderness developed in the left elbow, and the next day in the left shoulder. These symptoms soon subsided.

The patient's terminal week of life was characterized by episodes of acidosis, respiratory difficulty and decreasing urinary output. Five days before death she had a sore throat, enlarged submaxillary glands and leukocytosis (white-cell count of 17,100). The hemoglobin was now 6 gm., and the nonprotein nitrogen 150 mg. per 100 cc. Two days later she complained of severe pain under the right costal margin and below the right breast. On the day of death she was tremorous, twitching and delirious. There were bronchial to bronchovesicular breath sounds throughout the chest and increased spoken voice sounds and bronchophony over the right lower lobe. Death occurred on the forty-eighth hospital day.

Differential Diagnosis

Dr. Charles H. Du Toit*: The main theme of this case is hypertensive renal disease, progressing rapidly to death from uremia. As is often the case, the signs and symptoms of uremia itself overshadow evidence that might have pointed to the etiology of the kidney disease. The intriguing problem is that of relating the history of joint disease to the kidney disease. It is quite possible that these two conditions were totally unrelated, in which case one would make two diagnoses: rheumatoid arthritis and chronic glomerulonephritis. We would have to discuss, at some length, other conditions that are primarily classified as cardiovascular renal. Instead, I shall relate the two conditions by discussing the diffuse connective-tissue diseases. There are indeed a few logical reasons, as well as the sporting instinct, for going ahead with this approach.

In the first place the signs of kidney disease followed shortly after the first attack of arthritis. The terminal course was somewhat unusual for most chronic kidney diseases. The fact that on admission the patient was symptomatically more ill than the degree of uremia or the degree of hypertension would lead one to guess could point to a diffuse process. There was a definite suggestion that an acute process supervened. There was marked increase in the hematuria and in the amount of protein excreted in the urine. There was further elevation of blood pressure, which took place while the patient was under observation. These changes are not too frequently seen in chronic glomerulonephritis, in which the patient is apt to remain in relatively good health until immediately before terminal decompensation. Indeed, muscle tenderness and joint pains were observed in the later part of the disease. One would like to strengthen the case for multisystem involvement on the basis of pericarditis, gallop rhythm, possible pleuritis and the involvement of the right lower lobe of the lung; however, these things occurred so late that they really cannot be considered as having too much diagnostic significance.

There are a number of ways in which the joint and kidney diseases could be related. My attention is immediately drawn to the gold therapy, which preceded rather closely the evidence of onset of nephropathy. It is true, indeed, that gold is nephrotoxic, both when used therapeutically and in experimental animals. In a few cases it has been described as producing a picture not too dissimilar to acute glomerulonephritis, occasionally followed by a nephrotic component. However, these changes have appeared to be completely reversible. I could find no account in the literature of any progressive kidney damage occurring with gold therapy. The gold therapy still should be considered because certain other conditions, which I shall discuss in a moment, are known either to be exacerbated by or even to appear for the first time after gold or other drug therapy. I shall mention briefly the fact that the patient had an adverse reaction to sulfonamides.

Starting from the premise that the original disease was rheumatoid arthritis, I should discuss amyloid nephrosis. There are certain things against amyloid nephrosis. The arthritis was not described as being severe and was not prolonged. At least half the patients with amyloid disease of the kidney are completely free of hypertension throughout the entire course of the disease. Hematuria is said to be relatively rare in amyloid disease. My impression is that amyloid nephrosis in patients with rheumatoid arthritis remains relatively asymptomatic until either a frank nephrotic syndrome or uremia appears; from then on the course is relatively progressive.

In the initial physical examination there was no mention of joint deformities. It would have been of help if x-ray films of the joints had been taken because rheumatoid arthritis even in a complete symptomatic remission often leaves behind evidence of its occurrence such as destruction of the cartilage and irreversible changes in the synovial tissue. One can often pick up x-ray changes or some slight limitation of motion in certain joints. The other connective-tissue diseases such as lupus erythematosus and polyarteritis, which frequently masquerade as rheu-

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matoid arthritis, are less prone to show permanent changes in the articular tissue.

The two conditions that seem to fit this case best are disseminated lupus erythematosus and polyarteritis nodosa. In lupus Dr. Castleman may find certain changes such as hematoxylin bodies and wire-loop changes in the kidney that are pathognomonic. The lupus-erythematosus cell is also fairly characteristic of this disease. I am more uncertain about what to include in the term polyarteritis nodosa. The views appearing in the literature nowadays are so divided that one gets the impression that the term may cover several different diseases, which in some cases seem to merge imperceptibly into lupus erythematosus. I do not think on the basis of the history and findings that it is possible with any degree of certainty to pick one of these two conditions. Polyarteritis of the classic Kussmaul type frequently is accompanied by peripheral neuritis; its course is apt to be punctuated by symptoms referable to gross infarctions of various organs, particularly the gastrointestinal tract, and occasionally others like the liver and pancreas. It often has a leukocytosis. Anemia is not too frequently seen, except late in conjunction with uremia.

Lupus erythematosus, on the other hand, has a more marked change in the hematologic picture with anemia, leukopenia and often thrombocytopenia. I shall not discuss the facial lesions and the characteristic rash, for they were absent and are in many cases of proved lupus. This patient from the time she was admitted to the hospital was too far along the road to uremia to allow one to draw much help from the blood picture. In fact the white-cell count was normal. Although there was an anemia, it would be expected at this stage of any kidney disease. It would be very helpful if we knew more about the interval history of this patient. For instance, what was the blood picture? What was the blood pressure from the time she was first hospitalized with arthritis fifteen years previously and during the two previous hospitalizations? Such information would be more helpful in the making of a positive diagnosis. The absence of a positive LE phenomenon does not really help one way or another, since many examinations may be necessary before one is convinced that this phenomenon is present or absent. There is one point against lupus — that is, the normal albumin-globulin pattern. It would also be unusual in polyarteritis, but perhaps this is a little more in keeping with polyarteritis than with lupus.

I can think of two possible explanations of the change in the renal picture. In a Kussmaul type of polyarteritis, with necrotizing lesions in relatively large arteries, — usually in the bifurcations of arteries as they enter viscera, particularly the kidneys, — there might be a sudden increase in hematuria and declining renal function in association with a renal infarct. The other possibility is an active diffuse glomerulitis, which I think would be much more in keeping with lupus erythematosus although in some of the more diffuse vasculitides that go under the name polyarteritis the same condition occurs. Most cases falling into the latter classification have had fulminating courses and would not ordinarily have remissions and exacerbations for fifteen years.

On the whole, I am inclined toward disseminated lupus erythematosus because the age and the sex of this patient fall into the group that contains the maximum number of cases of lupus. The course, by and large, would fit better with lupus erythematosus than with any of the conditions usually classified as polyarteritis: it was smoldering and indolent, without evidence of gross changes in several organs, and it persisted for several years and then rapidly progressed.

I should make a brief comment on the findings in the right lower lobe of the lung. I believe they appeared subsequent to the x-ray film that is available. For a number of years Dr. Walter Bauer and his associates have pointed out that frequently lupus erythematosus terminally is complicated by bronchopneumonia or even a lobar pneumonia. More recently it has been suggested at the Mayo Clinic[1] that there is a fairly well definable pulmonary lesion in lupus erythematosus. Since a pneumonic picture such as this is a frequent terminal event in many diseases it is at best a rather weak point in favor of lupus.

DR. JACOB LERMAN: I should like to say that the history emphasizes the albuminuria and edema so much that it gives credence to the idea of long-standing amyloid nephrosis.

DR. DU TOIT: Does amyloid nephrosis come and go the way this did? I was rather impressed by references to periorbital edema with lupus erythematosus in the exhaustive review by Harvey and his associates.[2] It is becoming clear that episodes of the true nephrotic syndrome are very common in lupus erythematosus. I passed over amyloid disease for the reasons given. I do not recall that with amyloid disease the nephrotic syndrome is apt to have remissions, which do occur in lupus erythematosus. One wonders whether the episode six months before admission to this hospital was actually a true nephrotic picture. The nephrotic syndrome was not present on admission here.

DR. BENJAMIN CASTLEMAN: Dr. Strauss, would you like to comment?

DR. MAURICE B. STRAUSS: I am impressed by the fact that the kidneys were described as contracted six months before admission. Although amyloid kidneys can be secondarily contracted they are generally rather large. Against pure amyloid nephrosis, there is a relatively normal serum albumin value. If it were not for the fact that at conferences of this sort there is a predilection for the unusual, I should wonder whether this was not a case of chronic glomerulonephritis that ran a fairly usual course with secondary hypertension and nephrosclerosis.

Clinical Diagnoses

Uremia.
Chronic glomerulonephritis.
?Lupus erythematosus.
Rheumatoid arthritis.

Dr. Charles H. Du Toit's Diagnosis

Disseminated lupus erythematosus.

Anatomical Diagnoses

Chronic glomerulonephritis.
(Uremia.)
Uremic pneumonitis.
Cardiac hypertrophy.
Parathyroid hyperplasia, secondary.
(Rheumatoid arthritis.)

Pathological Discussion

Dr. Castleman: We have often been accused, Dr. Strauss, of presenting the exotic here. On occasion we do. If we had been handed the material of this autopsy without knowing anything about the history of the case, we should have reported this as a case of ordinary chronic glomerulonephritis and probably would not have presented it at this conference because it was too clear cut. When I was asked to review this case as a possibility for a clinicopathological conference because it had caused so much difficulty on the ward I agreed that it was an excellent teaching case. Pathologically, it was a straightforward case of chronic glomerulonephritis. Each kidney weighed about 100 gm. and had the coarse granular appearance characteristic of a contracted kidney. The cortex was reduced to almost half its width. We looked carefully for evidence of the connective-tissue diseases, but there were no wire loops, no hematoxylin bodies and no fibrinoid change. We looked equally carefully for evidence of arteritis and found none at all. Further evidence that she had long-standing renal insufficiency was the presence of secondary hyperplasia in the parathyroid glands and very mild renal osteitis fibrosa. There was no external evidence of rheumatoid arthritis, and the joints were not examined.

A Physician: Did she have pneumonia at death?

Dr. Castleman: In many places the alveoli were filled with red blood cells and inflammatory cells — findings that are often seen in uremia and called uremic pneumonitis. There was 300 cc. of fluid in each pleural cavity.

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CASE 41282

Presentation of Case

A nine-year-old girl was admitted to the hospital because of a "lump on her left leg."

Six months before entry she turned the left ankle. After this she complained of mild pain and had slight swelling on the lateral aspect of the ankle. However, she continued to walk on the leg. Five weeks later the ankle was again injured, with resultant pain of one week's duration. Six weeks before admission the swelling began to increase, but there was no increase of pain. There was no history of fever or weight loss.

Figure 1. *Anteroposterior, Oblique and Left Lateral Views of the Left Ankle, Showing Localized Expansion of the Distal Fibular Shaft, with Marked Thinning of the Cortex and Fine Trabeculations Traversing the Rarefied Area. The epiphysis is not involved.*

The patient was referred to this hospital for management.

The past and family histories were noncontributory.

Physical examination was negative except for the presence of a swelling, 5 by 2.5 cm. in diameter, involving the distal fibula. The mass was nontender, and no bruit was audible over it. The skin and subcutaneous tissue could be moved freely over it. The ankle showed full range of motion, and muscle power was normal. The skin temperature was 95°F. over the left and 92°F. over the right lateral malleolus.

The temperature was 98.6°F., and the blood pressure 110 systolic, 62 diastolic.

Urinalysis was negative. Examination of the blood revealed a hemoglobin of 14.4 gm. per 100 cc. and a white-cell count of 6200, with 67 per cent neutrophils. The blood sedimentation rate was 16 mm. per minute. The serum calcium was 10.7 mg., the phosphorus 4.1 mg., and the alkaline phosphatase 7.9 units per 100 cc. An intradermal tuberculin test, 1:10,000, was negative after twenty-four and forty-eight hours. An x-ray film of the chest was normal.

Films of the left leg revealed an expansile lesion of the distal diaphysis of the fibula measuring 5.5 by 2.5 cm. in maximal dimensions and extending to the metaphysis (Fig. 1). The cortex was extremely thin. Fine trabeculation was noted within the area of expansion. The edges of the defect were sharp, and the bone above it was of normal texture and density. A film of the right leg showed no abnormality. On the third hospital day an operation was performed.

Differential Diagnosis

Dr. Paul M. St. Aubin*: As stated in the protocol the radiogram shows a uniform fusiform lesion in the left fibula. The cortex is markedly thinned but has no apparent break in it. Triangular wedges of bone are seen joining the swelling to the normal shaft. Within the area of lessened density, which occupies the widened portion of bone, there are septums that have the appearance of loculated areas separated by bone walls. The epiphysis and epiphyseal line are intact. The soft tissue over the area of the lesion does not appear swollen on the radiogram.

I can interpret the swelling of the leg, at the time of the x-ray examination, as having been mostly due to the bony lesion itself, since soft-tissue swelling though present was minimal. I assume that the skin was not discolored.

Initially, I can exclude this lesion as being a local manifestation of a generalized disease since there was no evidence of disease elsewhere in the body and the history certainly indicated that the process was localized to the distal end of the fibula.

The history and appearance of the lesion clinically do not suggest an inflammatory process. Tuberculosis can produce cystic lesions in bone, with little or no bone reaction. But the tuberculin test was negative, and certainly a tuberculous lesion of this size would have had more sharply defined cavities and more bone reaction and no doubt would not have spared the epiphysis. Ecchinococcus cyst is rare and is hardly likely at this age, in this location and in this area. Moreover, this cystic bone lesion would not have spared the cortex this long.

I can safely say that the cyst originated in the medulla of the distal shaft of the fibula. Was this lesion benign or malignant? We know that it had been present for six months, and the careful molding of the bone indicates that it must have been present a good many more months. If this lesion had been malignant it is unlikely that the cortex or periosteal replacement would have been spared for so long a time and that the lesion would have been limited by the epiphyseal line. The bone reaction seen on the films, consisting of well organized triangular structures joining the widened shaft to the normal shaft, represents stress wedges necessarily built up for mechanical support. They might make one think of Codman's reactive triangle, but they do not represent this. The outer margins of these wedges are continuous with the thinned cortex and are certainly not evidence in this case of a malignant process. The soft tissues overlying the lesion give no radiologic evidence of swelling or disruption, and there was no clinical evidence of soft-tissue invasion as judged from the description of the skin overlying the mass and the normal motion and muscle power of the foot. The slightly elevated skin temperature over the lesion, if it was significant, suggests a rapidly growing malignant tumor, but a vascular benign tumor could produce a similar temperature elevation. I assume that the recorded skin temperatures represented the average of a series of readings. It would be important to know, since a 3°F. difference of temperature could obviously result from the errors in the procedure. The radiographic evidence is that of a benign lesion arising from the medulla of the distal fibula, and since clinical evidence does not suggest a malignant tumor, we shall assume that the lesion was benign.

A number of benign tumors can be eliminated from consideration. The patient's age and lack of fusion of the epiphyses rules out the possibility of a giant-cell tumor. Nonosteogenic fibroma is a possibility, but these tumors are usually eccentric and never involve the entire width of the shaft. In addition they are usually separated from the epiphyseal plate by a distance of several centimeters at least when they have reached this size. This tumor had been growing for quite a while and certainly would have moved up the shaft if it had been a nonosteogenic fibroma. The ovoid areas of translucency of a fibroma are sharply delineated and enclosed by a mantle of sclerotic bone, and the tumor does not tend to expand the bone.

An enchondroma can result in a radiographic appearance similar to this, but usually the septums and inner cortical margins are more sharply defined, and mottled areas of calcified cartilage can be seen within it. It is unlikely that the epiphyseal plate would have been spared this long with the tumor immediately adjacent to it. Moreover, many enchondromas arise from the epiphyseal plate. Actually, the location is uncommon for an enchondroma, which more often is seen in the upper femurs, humeri, metacarpals, metatarsals and phalanges.

Monostotic fibrous dysplasia can produce a cystic bone lesion with expansion and cortical erosion, but it is seen mostly in the third decade of life. It appears at the end of the first or beginning of the second decade, but does not manifest itself with symptoms until the third decade. It would not have reached this size in the first decade.

The two remaining possibilities are a simple bone cyst and an aneurysmal bone cyst. Both appear in childhood and adolescence prior to the closure of the epiphyses. The simple bone cyst originates near the epiphysis. After trauma, producing small fractures

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and following the healing of these fractures, normal bone forms in the metaphysis, and the cyst moves down the shaft away from the epiphysis. It is unilocular but can appear multilocular, as the result of the ridges along the inner cortical wall. The appearance of septums and trabeculae in the x-ray films of the case under discussion could certainly be explained by this lesion. The failure of the lesion to enter the epiphysis is characteristic. Thus, epiphyseal growth is unaffected. However, the simple cyst is usually found at the proximal end of the femur or humerus, and rarely in the distal fibula.

The aneurysmal bone cyst initially described by Jaffe and Lichtenstein[1] in their paper on unicameral bone cyst in 1942 has a radiologic appearance similar to the simple cyst. I do not believe I have ever seen an aneurysmal bone cyst. It presents as a well delineated, rarefied area of bone expansion with fine and coarse trabeculae, more numerous about the edges, giving the lesion a soap-bubble appearance. We certainly have that appearance in this lesion. Although usually eccentric in position, it produces symmetrical expansion when it is found within the smaller long bones. The cortex is so markedly thinned, according to Lichtenstein,[2] that it is frequently disrupted and replaced by a thin shell of periosteal new bone, which is not laminated. Radiographically, I doubt that anyone could differentiate this from very thin cortex. Obviously, the thin cortex in an expanded area of bone is really new bone that has been laid down and not cortex that has been pushed out. The end of the shaft is the usual location in long bones, and if the epiphyseal plate is present, the lesion is adjacent to it on the diaphyseal side. The tumor does not extend into the plate and affect it. According to Dahlin and his associates[3] the fibula is a rather frequent site for the aneurysmal bone cyst although it did not appear as a site in either of the papers by Lichtenstein.[2,4]

Since all the lesions mentioned above can mimic each other in the radiogram the differential diagnosis, from the appearance of the lesion itself, is difficult if not impossible. Considering all the factors involved, I can narrow my consideration down to the last two possibilities.

The location is common for an aneurysmal cyst and sporadic for a simple cyst. The multilocular — I am assuming it was multilocular from its appearance — soap-bubble nature of the lesion, together with the lack of sharpness of the inner cortical wall, — an important point, — is more in favor of an aneurysmal bone cyst. I cannot ignore the slight but obviously recorded skin-temperature difference, which would be more in favor of an underlying vascular tumor.

My first choice is an aneurysmal bone cyst. A very unlikely second choice is a simple bone cyst.

Clinical Diagnosis

Aneurysmal bone cyst of fibula.

Dr. Paul M. St. Aubin's Diagnosis

Aneurysmal bone cyst of fibula.

Anatomical Diagnosis

Aneurysmal bone cyst of fibula.

Pathological Discussion

Dr. Benjamin Castleman: At the time of the operation the surgeon unroofed the thin cortex and disclosed a multilocular lesion, each of whose locules were filled with blood. He then resected and curetted most of the lesion. The lesion had a cavernous appearance, containing sinusoidal-like structures, some of which were lined with thin endothelial-like tissue and others with fibrous connective tissue. That is apparently a characteristic appearance. The important point is that this lesion should not be mistaken for a giant-cell tumor. Very often these lesions do have many giant cells — because the blood in the cavernous areas excites a giant-cell reaction. These giant cells are not the same type seen in a giant-cell tumor; they are much smaller, have fewer nuclei and are found in the region of the hemorrhage.

What the aneurysmal bone cyst is, we really do not know. It is not a hemangioma; it may be somewhat like an arteriovenous shunt although no bruit is heard over it. The histology certainly does not suggest a new growth of any sort. It is perfectly benign. As Dr. St. Aubin mentioned, the giant-cell tumor rarely if ever occurs before the age of twenty. Whenever a lesion that is called a giant-cell tumor is found in a child, that diagnosis should be looked upon with great suspicion, for the lesion is more likely a cyst that has fractured and has produced a giant-cell reaction, an aneurysmal bone cyst or even a non-osteogenic fibroma of bone, which often stimulates bone formation, with giant cells.

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ANNUAL MEETING OF AMERICAN MEDICAL ASSOCIATION

A GOOD medical program, embellished by all the contemporary devices of audiovisual education and acres of technical, commercial and scientific exhibits, attracted an attendance of more than 11,000 physicians to Atlantic City for the hundred and fourth annual meeting of the American Medical Association, June 6-10. Probably most of those in attendance took little active part or interest in the deliberations of a few hundred delegates, council members, trustees and officers who held daily conclave at the Hotel Traymore, the official headquarters.

It is the decisions arrived at by the House of Delegates, however, that give the American Medical Association its distinctive flavor in the minds of the public. That these decisions are democratically arrived at is promptly apparent to any physician or layman who chooses to attend the sessions of the House of Delegates, or the many reference-committee hearings, all of which are open to the public and at which anyone may command a hearing. If the committee reports and the policies of the American Medical Association reflect only the opinions of those who are interested enough to share in their formation, the nonparticipant has no basis for complaint.

Two years ago the House of Delegates delayed action on the report of the Committee to Study the Relations Between Osteopathy and Medicine that medicine as currently taught in schools of osteopathy was not to be regarded as the teaching of cultist healing (hence, physicians might teach and consort with osteopaths without violating the *Principles of Ethics.*) In June, 1954, the Committee was instructed to justify this opinion by further inspection of osteopathic schools. At Atlantic City it confirmed the original recommendation. The reference committee on medical education and hospitals (to which the study committee's report was again submitted) was not satisfied that education in osteopathic schools was free of cultism. It suggested, however, that physicians might ethically teach in osteopathic schools. This the House of Delegates refused to accept, and a minority report was adopted instead, the effect of which was to nullify the work of the study committee and to leave the next step up to the osteopaths, whenever they see fit to delete the "osteopathic concept" from their teaching program.

The reports of Massachusetts delegates, Charles G. Hayden, chairman of the Committee on Legislation and Public Relations, and Norman A. Welch, chairman of the Committee on Miscellaneous Business, were adopted and widely commended. Among other things Dr. Welch's committee disapproved Section 8 of Chapter I of the *Principles of Medical Ethics,* which only a year ago declared it unethical for a physician to participate in the ownership of a drugstore in his medical practice or to dispense drugs or ap-

pliances unless adequate facilities were otherwise unavailable, and substituted a simple statement that it is not unethical for a physician to prescribe or supply drugs, remedies or appliances as long as there is no exploitation of the patient.

Dr. Hayden's committee reaffirmed opposition to extension of the Doctor Draft Law and was critical of the utilization of reserve medical officers in caring for the dependents of service men. It was further pointed out that the reasons for opposition of the American Medical Association to compulsory inclusion of doctors under Social Security should be made more widely familiar to physicians, who in many quarters (such as Michigan and the Charles River District of the Massachusetts Medical Society) have requested participation on a voluntary basis. Experience shows that voluntary participation in any Government-sponsored welfare plan tends sooner or later to compulsion.

Parts of a locally sponsored resolution critical of the publicity methods used in announcing the results of the Salk-vaccine evaluation study were included in a general approval of governmental policy, but supporting allocation on a voluntary basis rather than under governmental control and only inferentially criticizing the so-called "television method" of making initial announcements of medical discoveries.

Adequate comprehension of what lies behind the official attitude of the American Medical Association in controversial matters can only be obtained from a careful reading of the published proceedings in the *Journal of the American Medical Association*. These are long and complicated, but should be read by every physician simply as a means of obtaining first-hand information.

"HOBGOBLIN OF LITTLE MINDS"

Consistency, one of the more elusive virtues, is defined by Webster as "firmness of constitution or character; persistency," and as "harmony of conduct with profession; also, uniformity, as of practice." It is an admirable quality; a certificate of sound character. One knows where a thoroughly consistent person stands — if it is possible to be thoroughly consistent. Consistency, however, is one of those relative attributes that is rarely all one thing or another, although different persons may have strong leanings in either direction.

One of the main supports of logic, which can hardly stand proved without consistent argument, consistency is also, in a way, logic's goal. It is the apotheosis of sound reasoning. The question may be raised whether attainable or unattainable goals have the greater value, but that, in a way, is beside the point. Certainly goals attained have a faculty of shrinking into relative insignificance, and so it well may be with consistency.

To the degree that consistency is attainable it represents the result of direct and careful thought — somewhat limited, it is true, but conveying the sense of security that is frequently the accompaniment of limitations. It is man's need of the protective mechanism of consistency that forces his thinking, when possible, to proceed along a straight line with the undeviating co-ordination of a centipede, and with the same pedestrian qualities.

That this consistency of locomotion is not inevitable, however, is suggested by Mrs. Craster's "Pinafore Poem":

> The centipede was happy quite
> Until a toad in fun
> Said, "Pray, which leg goes after which?"
> That worked her mind to such a pitch,
> She lay distracted in a ditch,
> Considering how to run.

Consistency, according to some forgotten maker of aphorisms, is indeed a jewel.

A devotion to consistency carries also its penalties in the way of rational unimaginativeness — a lack of spiritual buoyancy and a renunciation of intellectual freedom that constitutes almost a rule of conduct for many persons. In journalism other risks are encountered, for the writer or editor is caught in the web of his own words, his lack of consistency is apparent and inescapable, and the harder he squirms the faster he is held.

These difficulties are encountered in any attempted adherence to static editorial policies, to the selection and classification of material and even to the following of firm regulations in regard to the acceptance of advertising copy. Should a given paper be classed as an original article, a special article, a report of progress or under medical intelligence? Sometimes the rule seems absolute; at other times expediency rather than consistency takes precedence, and the tune must be played by ear — sometimes more effectively than by note. Inconsistency, like adversity, also has its uses, and enough flexibility must be maintained to permit repeated violations of what more rigid minds would consider as irrefrangible tenets.

As Emerson wrote, "A foolish consistency is the hobgoblin of little minds, adored by little statesmen and philosophers and divines."

ANNUAL REPORT OF MASSACHUSETTS MEDICAL SERVICE

The annual report for 1954 of Massachusetts Medical Service contains information and constructive reasoning that will be of value to all interested persons, regardless of the Blue Shield plan in which they may be particularly interested. During the year enrollment rose from 1,551,433 to 1,686,565 members — an increase of 135,152 participants. The subscrip-

tion income rose from $21,202,842.07 to $24,014,-159.70, claim losses from $16,680,030.00 to $19,181,-709.00, and expenses from $1,396,662.20 to $1,488,-640.00. The expenses of approximately 6.2 per cent of subscription income represents a very low figure compared with those of most Blue Shield plans.

There has been an increasing shift from Plan A to Plan B with its greater benefits. Plan B now contains about 57 per cent of the members, and it is anticipated that equilibrium will be reached with 70 to 75 per cent of all subscribers in this category.

The vitally essential but somewhat revolutionary prolonged-illness certificate was put into effect in October, with 75,000 persons seeking its protection by the end of the year. Unique in this country, it has so far been offered only to special groups meeting stringent enrollment requirements. Two of the chief differences between the Blue Cross—Blue Shield certificate and the contract offered by private insurance companies are the lack of the costly "deductible" feature and the specification of insurable types of illness and verification of diagnosis by Blue Shield, which will tend to make it more economical and practical than similar coverage by private companies. The family charge was set at $24.00 until actuarial experience gives a better basis for the establishment of subscription rates, which, it is hoped, may be even less.

Another salutary innovation has been the reduction of the obstetric waiting period from twelve to the biologically traditional nine months. This seems to be a reasonable acceptance of one of nature's fundamental laws even at the estimated cost to the Service of $300,000 per year.

In another category is the still unsolved problem of caring for the aged, whose need for medical care is liable to increase as their employability decreases. The practice of both Blue Cross and Blue Shield has been to allow retiring employees to convert their insurance from group to nongroup coverage, although Blue Cross has found it necessary to provide fewer days of hospitalization than under group coverage. Further adjustments along these lines are almost sure to be necessary.

The outstanding value in a free society of an institution such as Blue Shield is its provision of service benefits on a broad, voluntary, medical-society basis, with free choice of physician within this wide range, as opposed to cash benefits or the closed medical panel. It must be continued and still further extended, for "it is a foregone conclusion that unless the people of this country get the kind of voluntary medical and hospital care insurance that they want they will vote themselves a compulsory program . . . One way or another they are going to achieve a large measure of security as far as medical and hospital bills are concerned. Under Blue Shield this means service benefits with reasonably high income limits, adequate schedules of fees, and control of policy matters by the medical profession itself."

Edinburgh Medical and Surgical Journal

This valuable Journal, for many years the sole organ of the medical profession in the Scottish metropolis, closed, with the April number, its separate and independent existence as a quarterly periodical. Henceforth it is to be united with the Monthly Journal, under the title of the "Edinburgh Medical Journal," which will be issued every month.

Boston M. & S. J., *July 19, 1855*

MASSACHUSETTS MEDICAL SOCIETY

COMMITTEE ON MATERNAL WELFARE

Anesthetic Accident with Anemia

A thirty-seven-year-old gravida III, para II, reported for prenatal care for the first time when 36 weeks pregnant. With a small android pelvis the first delivery (elsewhere) had been extremely difficult and was followed by sepsis. The second pregnancy was terminated by cesarean section elsewhere. The diet had been appallingly deficient in iron, with a resulting hemoglobin of 8.2 gm. per 100 cc. and a hematocrit of 28 per cent. She reported about 12 nosebleeds during the present pregnancy and, after a tooth extraction fourteen years previously, had been told that she was a "bleeder." A repeat cesarean section was elected, and it was decided to give blood as indicated during surgery. Preoperative sedation was given on schedule, but because operation was delayed further doses of scopolamine were administered two and three hours later. An intravenous drip was then started and she was moved to the anesthesia room, where she began to vomit. A Levin tube was passed with the removal of dark-green fluid. Thereafter, the patient was given 6 cc. of 2 per cent Pentothal Sodium (120 mg.), and administration of nitrous oxide, oxygen and ether was started. Five minutes later the temporal pulse was very weak, and no blood pressure could be obtained. The anesthesia was stopped; oxygen was given, and she was put in Trendelenburg position. Neo-Synephrine, 1.0 mg., intravenously, was given without effect and was repeated. Administration of whole blood was started under pressure. The apical rate was about 160. She continued to breathe and respirations were reinforced with oxygen under pressure. Mottling developed, and the fetal heart beat disappeared. Neo-Synephrine was added to the intravenous drip. Without improvement in an hour, she was turned on her side, to remove the uterine mass from the great vessels. With this the apical heart beat stopped, and after a few gasping respirations, these

too ceased. At about this time a cut down was done, and further blood under pressure was given to a total of 1000 cc. Fifteen minutes after the heart sounds ceased the chest was opened for cardiac massage. A hand was passed around the heart, which was found to be small and contracted in systole, without motion. Massage was ineffectual, and the patient was officially pronounced dead.

The only significant post-mortem finding was massive, bilateral pulmonary atelectasis, the distribution and extent of the lesion indicating that it was truly ante mortem and had not resulted from opening of the chest. The pericardium and anterior wall of the right ventricle were torn. From the appearance of these defects they were interpreted as post-mortem phenomena, having occurred during the surgical procedure immediately after the patient had died.

This case was classified as a preventable death in the class of anesthetic accidents. The cause of death was finally judged to be a toxic effect of the anesthetic agent superimposed on a severe secondary anemia. The primary avoidable factor, of course, was anemia.

The first and most important aspect of this case is the clearly demonstrated secondary anemia. This had been fully recognized, and surgery had been delayed to permit its study and treatment. Treatment, however, had been limited by circumstances to a month, and only slight improvement had resulted. Medical consultants recommended preoperative transfusion for this reason, but this advice was overruled by the rationale that transfusion in late pregnancy is too dangerous. It is now the consensus that, with careful crossmatching and other standard safeguards, the risks have been so reduced as to be less than those of anesthesia and surgery in the presence of anemia. The case under discussion certainly seems to prove that adequate transfusion should have been given in advance.

The second issue is the choice of anesthetic agent. Many believe that a drug of known high toxicity should not be given in the presence of anemia. Certainly, the supplementation with nitrous oxide was extremely unwise. It is conceivable that even so dangerous a drug as Pentothal might not have been lethal in the extremely small quantity given if there had been no addition of nitrous oxide with its further demands on the already limited oxygen-carrying capacity of the patient. There seems to have been no reasonable contraindication to spinal or other regional anesthesia in this case and one wonders why it was not used.

Finally, there is no satisfactory explanation for the atelectasis unless it arose somehow from the prolonged period of collapse, during which extensive but vain efforts at resuscitation were made.

JOHN FIGGIS JEWETT, M.D.
Chairman

DEATHS

BRAFF — Max M. Braff, M.D., of Brookline, died on May 7. He was in his sixty-fourth year.

Dr. Braff received his degree from the Boston University School of Medicine in 1917. He was a fellow of the American Medical Association.

He is survived by his widow.

DONAIS — Joseph Eusebe Donais, M.D., of Southbridge, died on May 17. He was in his seventy-ninth year.

Dr. Donais received his degree from Laval University Faculty of Medicine. He was a fellow of the American Medical Association.

BOSTON MEDICAL LIBRARY

JAMES F. BALLARD MEMORIAL FUND

That a lasting memorial would be established in honor of the late James F. Ballard was only natural, for this distinguished librarian left behind him a host of grateful friends here and abroad.

One of the fellows of the Boston Medical Library has generously offered to start a James F. Ballard Memorial Fund with a contribution of $5,000. This contribution, however, is contingent upon significant interest in the Memorial Fund by other friends of Mr. Ballard and friends of the Boston Medical Library.

The income from the Fund will be used primarily to establish a pension plan for the personnel of the Library. This is a project that was dear to the heart of Mr. Ballard, who, with no personal wish to retire, even after sixty-three years of service, was considerably concerned over the lack of security for Library workers.

Because there is no pension plan in effect now and no funds available at the Library for such a plan, the James F. Ballard Memorial Fund not only will serve as a fitting and lasting tribute to Mr. Ballard but also will help to correct a most serious inadequacy in the Library's employee program.

Fellows and friends wishing to contribute to the Memorial Fund may do so by sending their checks, made payable to the Boston Medical Library, to the Library at 8 Fenway, Boston 15, Mass.

CORRESPONDENCE

YOO HOO

To the Editor: At this late date I have just read the article on the new disease (Yoo-Yoo) in the February 17 issue of the *Journal*.

Our consultant was recently presented with such a case and called it the "mumble-mumble" disease. This refers to the fact that he would mumble on how interesting and unusual the problem was and would surely desire a follow-up examination.

Since we should use the same nomenclature we will list it as you describe, but we are interested in the proper pro-

nunciation. A standardized method for saying it would eliminate the hazards involved and so allow us to use this term more freely. It could easily be seen that someone would say "you-you" and the person spoken to would madly shout back, "me-me?" This nonsense must be avoided!

WILLIAM MANDEL, M.D.
Officer in charge, Medical Service
3345 USAF Hospital
Chanute Air Force Base, Illinois

REGARDING THE BRICKER AMENDMENT

To the Editor: The Bricker Amendment is up for a rehearing in the current Senate Committee. It is predicted that the amendment of the treaty-making power of the Executive and the Senate, as well as the proposal that only by Congressional or state legislation or both can an Executive agreement become internal law, but that this legislation must be confined to the area of power specifically granted to the federal Government by the States in the Constitution, will not get out of committee this year.

Recalling the editorial in the February 18, 1954, issue of the *Journal* "Physicians or Politicians?" and the wise rebuttal to a letter from a good friend in the April 22, 1954, issue about the freedom of the press, I consider this a good time to comment on the wisdom of our councilors in giving approval to any future alignment of the American Medical Association with the supporters of the Amendment.

Is it fair to use the excuse that we are closing the door on socialized medicine by treaty by supporting the group backing the Bricker Amendment?

Arthur Krock recently pointed out that the power of one senator in combination with the authority of a third of the body to deny approval to a treaty is sufficient safeguard against abuses that, in prospect, are disturbing the advocates of the change. The general power of a majority of both branches to nullify Executive agreements by withholding the operating mechanisms, including money, is sufficient safeguard against abuse in that quarter.

Socialized medicine will not come in the back door as the result of the President's right to make international agreements but more probably by the reputation of the American Medical Association in the mind of the public as one of the most resistant organizations in the country. As a Society we should not give rubber-stamp endorsement to the political naïveté often exhibited at the top by the support given to groups in favor of the Bricker Amendment.

SAMUEL BACHRACH, M.D.
Worcester, Massachusetts

Note: One would be inclined to agree with Dr. Bachrach that there are matters of more vital concern to the profession and the nation than the Bricker Amendment. — ED.

DR. ELIZA TAYLOR RANSOM

To the Editor: Dr. Eliza Taylor Ransom, famous in women's medical circles, died on June 7 in Aberdeen, North Carolina. Born in Escott, Ontario, on May 31, 1863, she was the daughter of William G. and Janet Thomson Taylor.

She was a graduate of Oswego, New York, Normal School (1888) and Boston University School of Medicine (1900), with postgraduate work at Johns Hopkins University.

Dr. Ransom practiced medicine in Boston for forty years. After a study of the twilight-sleep method of painless childbirth in Freiburg, Germany, she established the first twilight-sleep maternity hospital in this country — on Bay State Road in Boston.

She was an active worker in the woman-suffrage movement and a charter member of the Professional Women's Club, the Business and Professional Women's Club and the Women's City Club. She organized the Women's Auxiliary of the Boston Evening Clinic and was a member of the Copley Society, Canadian Club of Boston, Boston University Women's Graduate Club, Massachusetts Homeopathic and other medical societies. She was the author of many articles in medical journals on the subjects of mental and nervous diseases and of childbirth.

Her husband, George W. Ransom, was a prominent educator, and was probably best known in Boston as the master of the Abraham Lincoln School. He organized the first civics classes in Boston settlement houses in the early 1900's, and was advisor to their leaders.

Dr. Ransom is survived by two daughters, Mrs. Gordon F. A. Fletcher of Bronxville, New York, and Mrs. Benjamin C. Mayhew of Chilmark, Martha's Vineyard, a brother, William C. Taylor of Detroit, Michigan, and two sisters, Mrs. Forrest Fulton and Miss Agnes J. Taylor, of Purlock, California.

ELEANOR RANSOM MAYHEW
Chilmark, Massachusetts

BOOK REVIEWS

Neurology. By S. A. Kinnier Wilson, M.A., M.D., D.Sc. (Edin.), F.R.C.P. Edited by A. Ninian Bruce, F.R.C.P. (Edin.), D.Sc. (Edin.), M.D., F.R.S. (Edin.), Lt.-Col. R.A.M.C., consulting physician, Bangour Mental Hospital and St. Andrew's Hospital, Hawick, consulting neurologist, Jordanburg Nerve Hospital, Edinburgh, lecturer in neurology, University of Edinburgh, member, Association of British Neurologists, honorary member, American Psychiatric Association, membre correspondant étranger, Société de Neurologie de Paris, membre associé étranger, Société Médico-Psychologique, Paris. Second edition. In 3 volumes. 4°, cloth, 2060 pp., with illustrations. Baltimore: Williams and Wilkins, 1955. $27.50.

When the first edition of this book was published in 1940 it was reviewed in the *Journal* for July 11 with special editorial comment as one of the outstanding books on the subject. Indeed, it could only be compared with the previous text by Oppenheim, published in Berlin in 2 volumes in 1894 and skillfully translated into English in 1911, that had been the standard book on neurology since the date of publication. The late Kinnier Wilson, who died just before the 1940 edition of his book was issued, was particularly equipped to write a comprehensive textbook of this type, but more important still, his large experience in practice, his discernment in the evaluation of neurologic diseases and his concise style of writing gave the book the distinct stamp of his particular personality. There was little for the editor, Ninian Bruce, to add at that time. However, the subject has expanded so rapidly and grown so vast in the fifteen years intervening since the first edition that no editor can possibly keep up with the mountainous waves of publications. The age of the great textbook by a single physician has long passed and has been succeeded by the age of the monograph.

In spite of this sound tendency of the times the new edition of 1955 makes a brave attempt to bring neurologic literature up to date, with only partial success, for even the enumeration of papers of significance is too much for any one man. Only a group of scientists, sifting and evaluating the literature month by month, could be expected to eliminate the nine tenths and save the basic tenth that should find its way into a modern textbook. The present editor has added a partial list of contributions published since 1940, but the full evaluation of their worth, so strikingly present in the primary work of Wilson, leaves much to be desired. Some references are found in the text and not in the bibliography. Citations have been taken out of the footnotes and placed at the end of the first volume and thereby made less easy to use. Notations of papers of minor value appear alongside those of real importance.

To offset an omission in the 1940 text the editor enlisted the help of Sir Russell Brain, who has provided a splendid chapter on aphasia, apraxia and agnosia. Wilson apparently had not left notes for such a chapter at the time of his death, and this deficiency has been amply made up in the present edition. In addition, Dr. Nevin has revised the chapter on neurosyphilis and rewritten the section on treatment. The book is published in 3 volumes, making it less convenient to use than the 2 volumes of the previous edition.

The type and paper are not quite so pleasing, and the index is less adequate. In spite of these deficiencies this work will be welcomed by neurologists, for it still contains the best of Wilson's ideas in a permanent form, and no one in modern times knew more about current neurology, or could present it in a more acceptable form.

HENRY R. VIETS, M.D.

The Child, His Parents and the Physician. By Hale F. Shirley, M.D. 8°, cloth, 159 pp., Charles C Thomas, 1954. $3.75. (Publication No. 205, *American Lecture Series.*)

Here is a book about a very important triangle and certainly one to which more attention should be given. It happens that the author is professor of pediatrics and director of the Child Psychiatry Unit at Stanford University School of Medicine. This is an unusual combination because most pediatricians are not psychiatrists and vice versa.

This book gives promise that more can be done on earlier levels of integrated preventive psychiatry instead of too late as in some cases, when the work even the best psychiatrist can do for an adult neurotic is along the lines of a repair job. Every practicing psychiatrist realizes the fact that the personality is set on its foundations at an early date, and all therapists looking backward can see points along the production line where more effective modifications might have been worked out *if* (an enormous if) the forces impinging on the growing personality of the person had been more favorable. This book gives the reader a workable point of view and provides an area of agreement for parents, teachers and physicians. Especially valuable are the second chapter, on the emotional needs of the child, and the sixth, on technics. In this book many parents, teachers and physicians will find well expressed the types of persons and the kinds of reactions with which they have to deal in everyday living.

MERRILL MOORE, M.D.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Fluid Therapy. By James D. Hardy, M.S. (Chem.), M.D., associate professor of surgery and director of the surgical laboratories, Medical College of the University of Tennessee, and diplomate, American Board of Surgery and American Board of Thoracic Surgery. 8°, cloth, 255 pp., with 77 illustrations. Philadelphia: Lea and Febiger, 1954. $5.50.

The author presents a complete discussion of the physiology of body-fluid metabolism and fluid therapy. He considers its use in surgical conditions, in infants, children and the aged, heart failure, diabetic acidosis, urology, neurosurgery and orthopedics, renal failure, burns, the management of blood loss, liquid alimentation and complications of intravenous fluid therapy. There is a good index, and the publishing is excellent. The book should be in all collections on the subject.

Klinische Fehldiagnosen. By Prof. Dr. M. Bürger, director, Med. Universitätsklinik, Leipzig. Second edition. 8°, cloth, 550 pp., with 214 illustrations and 55 tables. Stuttgart: Georg Thieme, 1954. DM 59.40. $14.15.

This treatise on mistaken diagnoses, first published in 1953, was received so favorably at home and abroad that this new edition was published. The whole field of internal medicine is covered, and there are special chapters on occupational diseases and poisoning, the locomotor system, internal medicine and gynecology and endocrinology. Throughout the text there are 209 case histories with the mistaken and correct diagnoses. There is a good index, and the publishing is excellent. This is a valuable book for the German-reading physician.

Some Account of the Pennsylvania Hospital. By Benjamin Franklin. Printed in facsimile with an introduction by I. Bernard Cohen. 8°, cloth, 40 pp., with illustrations. Baltimore: Johns Hopkins Press, 1954. $3.25.

Franklin's book has been out of print for over a hundred years and has become an expensive collector's item. It has now been made available at a low price in a fine facsimile. It is recommended for all collections on medical and general history.

Hysterectomy. By John C. Burch, M.D.; and Horace T. Lavely, M.D. 4°, cloth, 94 pp., with illustrations and tables. Springfield, Illinois: Charles C Thomas, 1954. $5.50. (Publication No. 226, *American Lecture Series.*)

The authors give a detailed description of the various types of operations, which are illustrated step by step by excellent halftone drawings. There is a good index, and the publishing is excellent.

The Auxiliary Heart. By William Walter Wasson, M.D. 8°, cloth, 184 pp., with illustrations. Springfield, Illinois: Charles C Thomas, 1954. $10.50.

This monograph presents the results of a study of the chest by x-ray examination during a period of thirty years for the purpose of evaluating the lesser circulation. References are carried as footnotes to the pages, and there is a supplemental bibliography of 13 pages. The literature is surveyed, and there are indexes of names and subjects. The seemingly high cost of the book is to some extent explained by the large number of expensive illustrations.

Lehrbuch der röntgenologischen Differentialdiagnostik. By Prof. Dr. W. Teschendorf, Köln. Vol. 2. *Erkrankungen der Bauchorgane.* Third edition revised. 4°, cloth, 1047 pp., with 1610 illustrations. Stuttgart: Georg Thieme, 1954. $44.30. (Distributed in the United States by Intercontinental Medical Book Corporation, New York.)

This second volume of a comprehensive treatise now in the third edition has been revised and brought up to date. It is devoted to diseases of the abdomen and its organs. References are carried as footnotes to the pages, and there is an extensive index. The set should be in all collections on radiology.

Röntgendiagnostik des Schädels. By Prof. Dr. Willy Loepp, assistant professor of roentgenology, Universität Königsberg (Pr.); and Prof. Dr. Reinhold Lorenz, professor, Universität Hamburg, and chief physician, Röntgeninstitut des Krankenhauses, Hamburg-Barmbek. 4°, cloth, 579 pp., with 696 illustrations. Stuttgart: Georg Thieme, 1954. DM 97.

This is a comprehensive treatise on the x-ray diagnosis of conditions of the head and skull. The authors discuss the normal skull, growth disturbances, congenital anomalies, mongolism and related conditions, endocrine, generalized salivary and salivary diseases, avitaminosis, parasitic and inflammatory diseases, benign and malignant tumors, fractures of the skull and base, the sella turcica, the temporal bone, accessory sinuses, orbit, symptoms of brain pressure, symptomatology, endocranium, jaws and teeth and special technic. The literature has been surveyed, and there is a bibliography of 16 pages. There are indexes of names and subjects; the publishing is excellent. This valuable book should be in all collections on the subject.

Die Wirbelsäulenverletzungen und ihre Ausheilung: Pathologische Anatomie, Klinik, Röntgendiagnostik, Begutachtungs-und Zusammenhangsfragen. By Prof. Dr. Alfons Lob, Sanderbusch/Oldbg. Second edition revised. 4°, cloth, 272 pp., with 149 illustrations and 16 tables. Stuttgart: Georg Thieme, 1954. $18.55. (Distributed in the United States by Intercontinental Medical Book Corporation, New York.)

This second edition of a special monograph on injuries of the spine and their treatment has been revised to bring it up to date. There is a bibliography of 8 folio pages. There is a good index, and the publishing is excellent.

An Historical Chronology of Tuberculosis. By Richard M. Burke, M.D., assistant professor of medicine, University of Oklahoma School of Medicine, and director of tuberculosis control, Oklahoma State Health Department. Second edition. 12°, cloth, 125 pp., with 6 figures. Springfield, Illinois: Charles C Thomas, 1955. $3.75.

The first edition of this book was published in 1938. In this new edition the author has incorporated the new drugs used in the treatment of tuberculosis and for the first time has included a bibliography of standard sources and a list of 476 references. There are indexes of authors and subjects. The book is recommended for all history collections.

The Year Book of Drug Therapy. (1954-1955 Year Book Series.) Edited by Harry Beckman, M.D., director, Department of Pharmacology, Marquette Schools of Medicine and Dentistry, and consulting physician, Milwaukee County General and Columbia hospitals, Milwaukee, Wisconsin. 12°, cloth, 592 pp., with 74 illustrations. Chicago: Year Book Publishers, 1955. $6.00.

The articles abstracted in this volume were taken from periodicals published between August, 1953, and August, 1954. They cover the whole field of medicine and its specialties. There are indexes of authors and subjects.

Textbook of Chiropody. By Margaret J. McKenzie Swanson, B. Litt., F. Ch.S., co-founder of Edinburgh Foot Clinic and School of Chiropody. Second edition. 8°, cloth, 268 pp., with 160 illustrations. Baltimore: Williams and Wilkins, 1954. $5.00.

The first edition of this British book was published in 1948. This new edition has been revised and brought up to date. The book is essentially a manual on diseases of the foot. The printing was done in Great Britain.

The Kidney. Edited by A. A. G. Lewis, B. Sc., M.D., M.R.C.P., and G. E. W. Wolstenholme, O.B.E., M.A., M.B., B. Ch., assisted by Joan Etherington. 8°, cloth, 33 pp., with 125 illustrations. Boston: Little, Brown and Company, 1954. $6.75. *(Ciba Foundation Symposium,* arranged jointly with the Renal Association.)

Twenty-one articles were read and discussed at this symposium. The papers were divided into five groups: structural and functional relations; tubular functions other than the regulation of acid-base balance; renal share in the regulation of acid-base balance; general problems of electrolyte excretion; and renal share in volume control of body fluid. Short lists of references are appended to the papers, and there are indexes of authors and subjects. The various symposia of Ciba are recommended for all medical libraries.

NONCLINICAL NOTES

HONORIS CAUSA

Dr. Theodore H. Ingalls, associate editor of the *Journal* and associate professor of epidemiology at the Harvard School of Public Health, was awarded an honorary degree of doctor of science on June 5 by Hamilton College, from which he graduated in 1929. Among the achievements for which Dr. Ingalls was cited are his outstanding contributions to the study of congenital defects and their origin.

APPOINTMENT OF DR. ULFELDER

Dr. Howard Ulfelder has been appointed as chief of staff of the Vincent Memorial Hospital, chief of the Gynecological Services of the Massachusetts General Hospital and clinical professor of gynecology at Harvard Medical School, to succeed Dr. Joe V. Meigs, whose retirement was announced in May. The joint appointment was announced by the trustees of the two hospitals and the dean of the medical school.

NOTICES

ANNOUNCEMENT

Dr. Julian L. Pearlman announces the opening of his office at 114 Waltham Street, Lexington, Massachusetts, for the practice of pediatrics.

ARMY MEDICAL SERVICE POSTGRADUATE COURSE

A postgraduate course on medical care of atomic casualties will be offered at the Walter Reed Army Medical Center, Washington, D. C. This year the course will be offered six times, instead of four times as in previous years. Dates for the courses still to be given are as follows: September 12-21, 1955; December 5-14, 1955; January 30-February 8, 1956; March 19-28, 1956; and June 4-13, 1956. Further information may be obtained from Department of the Army, Office of the Surgeon General, Technical Liaison Office, Washington 25, D. C.

NEW YORK ACADEMY OF MEDICINE GRADUATE FORTNIGHT

The twenty-eighth annual graduate fortnight of the New York Academy of Medicine will be held at the Academy, October 10 through 21. The subject of the meeting will be "Problems of Aging," and the program will consist of twenty evening lectures and four evening panel meetings, six morning panel meetings, visits to nineteen afternoon hospital clinics, a scientific exhibit, and visits to five Community Educational and Recreational Day Centers for the aged. Medical officers of the armed forces, interns and residents will be admitted without charge. Further information may be obtained from the Secretary, Graduate Fortnight, 2 East 103 Street, New York 29, New York.

SOCIETY MEETINGS AND CONFERENCES

JULY, AUGUST and SEPTEMBER. Beth Israel Hospital Course. Page 509, issue of March 24.

JULY 20–AUGUST 23. Consultation Clinics for Crippled Children in Massachusetts. Page 1099, issue of June 23.

AUGUST 28–SEPTEMBER 2. American Congress of Physical Medicine and Rehabilitation. Page 157, issue of January 27.

AUGUST 30 and 31 and SEPTEMBER 1. New England Health Institute. Page 1010. issue of June 9.

SEPTEMBER 12–21, DECEMBER 5-14, 1955, JANUARY 30–FEBRUARY 8, MARCH 19–28 and JUNE 4–13, 1956. Army Medical Service Postgraduate Course. Notice above.

OCTOBER 6–8. Academy of Psychosomatic Medicine. Page 509, issue of March 24.

OCTOBER 10–21. New York Academy of Medicine. Graduate Fortnight. Notice above.

OCTOBER 22–26. American Heart Association. Scientific Session. Page 603, issue of April 7.

OCTOBER 23–27. American Institute of Dental Medicine. Page 414, issue of March 10.

NOVEMBER 1–3. Henry Ford Hospital Symposium on Enzymes. Page 920, issue of May 26.

NOVEMBER 6–13. Second International Congress of Allergology. Page 157, issue of January 27.

NOVEMBER 11 and 12. Inter-Society Cytology Council. Page 1056, issue of June 16.

NOVEMBER 14–25. Course in Laboratory Diagnosis of Tuberculosis. Page 1102, issue of June 23.

NOVEMBER 19–21. American Association of Blood Banks. 8th Annual Meeting. Palmer House, Chicago, Illinois.

NOVEMBER 29–DECEMBER 2. Interim Session of the American Medical Association, Boston.

CALENDAR FOR THE WEEK BEGINNING THURSDAY, JULY 21

THURSDAY, JULY 21

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*9:00–10:00 a.m. Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.

*9:00–10:00 a.m. Arthritis Grand Rounds. Robert Breck Brigham Hospital.

*10:00–11:00 a.m. Combined Medical-Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.

10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*11:00 a.m.–12:00 m. Thoracic Conference. A Survey of Tumors of the Lung and Mediastinum. Dr. Harrison Black. Main Amphitheater, Peter Bent Brigham Hospital.

*11:00 a.m.–12:00 m. Medical Staff Conference. Sherman Auditorium, Beth Israel Hospital.

(Concluded on page xxvi)

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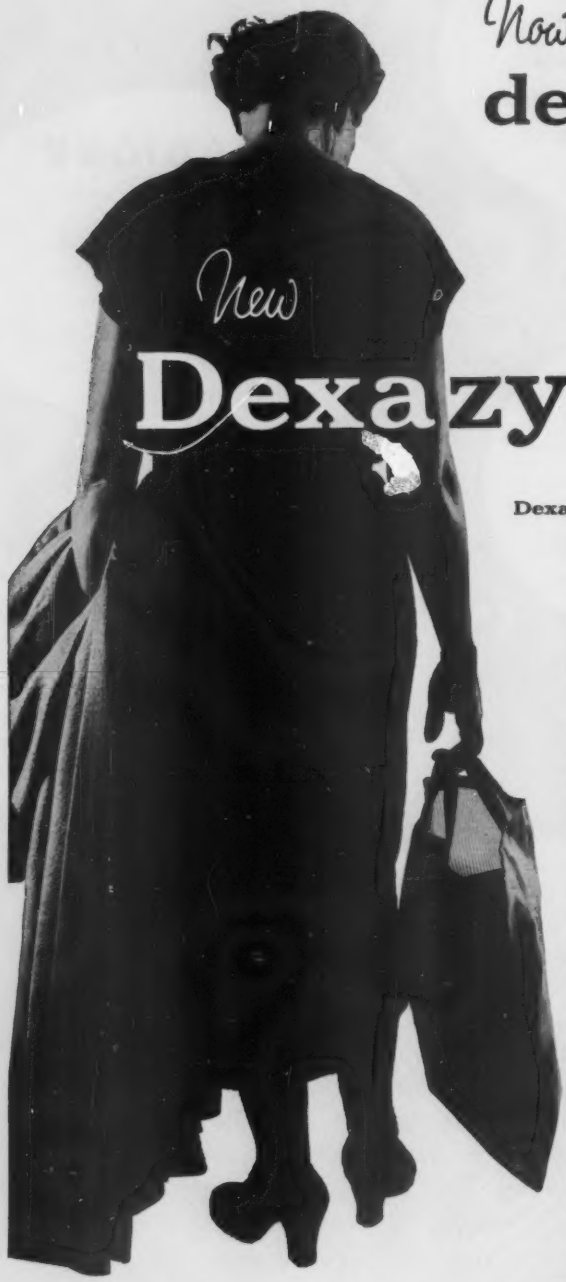

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Phosphorated Carbohydrate Solution

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IMPORTANT: **EMETROL must always be taken *undiluted.* Fluids should not be allowed for at least 15 minutes after each dose.**

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in epidemic vomiting (acute infectious gastroenteritis, intestinal "flu"), EMETROL works rapidly, even in refractory cases; control is usually established with the first few doses, "often with a single dose."[2]

1. Crunden, A. B., Jr., and Davis, W. A.: Am. J. Obst. & Gynec. 65:311, 1953. 2. Bradley, J. E., et al.: J. Pediat. 38:41, 1951. 3. Tebrock, H. E., and Fisher, M. M.: M. Times 82:271, 1954.

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for the patient with fever,

SF*

means (*Pfizer*) antibiotics, *fortified with vitamins*

to support recovery, speed convalescence

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the leading broad-spectrum antibiotic, discovered by Pfizer

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For patients with infections, "one must aim at maintaining the normal daily nutritional requirements, replacing previous depletions and current losses, and supplying whatever increased requirements may be related to the nature of the illness."[1] This is the concept of "treating the 'whole' patient."[2]

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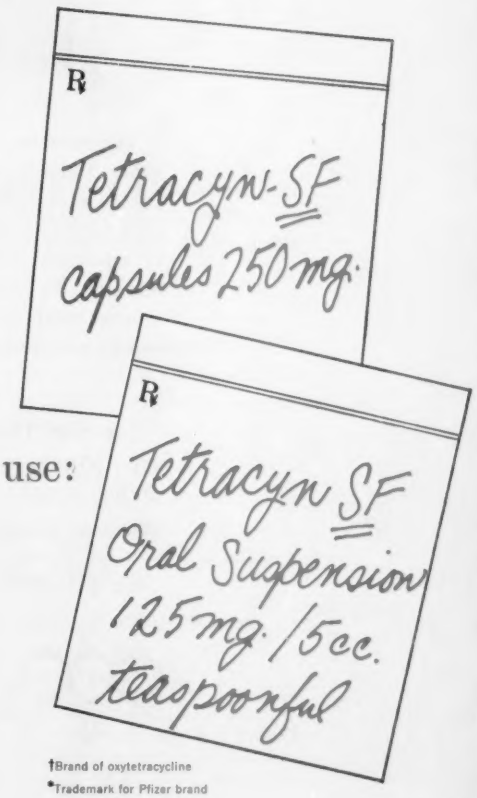

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Tetracyn SF and Terramycin SF are formulated to provide with the minimum daily dose of each antibiotic (1 Gm. of Tetracyn or Terramycin) the stress vitamin formula recommended by authorities on nutrition.[1]

1. Pollack, H., and Halpern, S. L.: Therapeutic Nutrition, Prepared in Collaboration with the Committee on Therapeutic Nutrition, Food and Nutrition Board, National Research Council, Washington, D. C., 1952. 2. Marti-Ibáñez, F.: Antibiotic Med. *1*:247 (May) 1955. 3. Dumas, K. J.; Carlozzi, M., and Wright, W. A.: Antibiotic Med. *1*:296 (May) 1955. 4. Milberg, M. B., and Michael, M., Jr.: Ann. New York Acad. Sc., In press. 5. Prigot, A.: Ibid.

†Brand of oxytetracycline

*Trademark for Pfizer brand of antibiotics with vitamins.

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Cohen, I.M.: Am. J.M. Sc. 229:355 (April) 1955.

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EPILEPSY

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1. Merlis, S.: DIAMOX: A Carbonic Anhydrase Inhibitor—Its Use in Epilepsy. Neurology. 4:11, 863-866 November 1954.
2. Becker, B.: Decrease in Intraocular Pressure in Man by a Carbonic Anhydrase Inhibitor, DIAMOX. Am. J. Ophth. 37:1, 13-15 January 1954.

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(Concluded from page 84)

*11:00 a.m.–12:30 p.m. Hand Clinic (Physical Medicine and Rehabilitation Service). Boston City Hospital.
*12:15–1:15 p.m. Tumor Clinic. Dr. T. W. Botsford. Amphitheater, Peter Bent Brigham Hospital.

FRIDAY, JULY 22
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*9:30–11:30 a.m. Medical and Surgical Grand Rounds. Drs. George W. Thorn and Francis D. Moore. Main Amphitheater, Peter Bent Brigham Hospital.
*10:00 a.m. Tuberculosis Surgical Clinic. South End Health Unit, 57 East Concord Street.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*1:30 p.m. Fertility and Endocrine Clinic. Free Hospital for Women, Brookline.
*1:30 p.m. Tumor Clinic. Mount Auburn Hospital, Cambridge.
*4:00–10:00 p.m. Alcoholism Clinic. By appointment. Washingtonian Hospital, 41 Morton Street, Jamaica Plain.

SATURDAY, JULY 23
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

MONDAY, JULY 25
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Medical and Surgical Clinic on Diabetic Problems. New England Deaconess Hospital.
*8:30–9:30 a.m. Clinic by Entire Surgical Staff and Anesthesia Staff. New Cheever Amphitheater, Dowling Building, Boston City Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*12:15–1:15 p.m. Clinicopathological Conference. Main Amphitheater, Peter Bent Brigham Hospital.
*1:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*4:00 p.m. Clinicopathological Conference. Pathology Conference Room, Beth Israel Hospital.
*4:00–5:00 p.m. Surgical Pathology. Dr. MacMahon and staff. Stearns Auditorium, New England Center Hospital.
*4:00–5:30 p.m. Anesthesiology Conference. Surgical Conference Room. Peter Bent Brigham Hospital.
*5:00–6:30 p.m. Anesthesia Group of the Lahey Clinic. Joslin Auditorium, New England Deaconess Hospital.
5:15 p.m. Staff Meeting. Harris Hall, New England Deaconess Hospital.
*7:00–9:00 p.m. Slide Seminar in Pathology. Dr. MacMahon and staff. Stearns Auditorium, New England Center Hospital.

TUESDAY, JULY 26
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*9:00 a.m. Geriatrics Clinic. Peter Bent Brigham Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*12:15–1:15 p.m. X-Ray Conference. Dr. Merrill Sosman. Main Amphitheater, Peter Bent Brigham Hospital.
12:30–1:30 p.m. Medical Journal Club. Joslin Clinic. (Cafeteria) New England Deaconess Hospital.
*5:00–6:00 p.m. Service Meeting followed by Clinical Conference (Medical, Surgical, Obstetrical). Faulkner Hospital.

WEDNESDAY, JULY 27
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*9:00–10:00 a.m. Surgical Grand Rounds. Massachusetts Memorial Hospitals.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m. Boston State Hospital Psychiatry Seminar. Reception Building Auditorium, 591 Morton Street, Dorchester.
*11:00 a.m. Orthopedic Grand Rounds. Bigelow Amphitheater, White 3A, Massachusetts General Hospital.
*12:00 m.–1:00 p.m. Pediatric Clinicopathological Conference. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
*12:00 m.–1:00 p.m. Roentgen Diagnostic Conference. 5th-floor teaching unit, Beth Israel Hospital.
*12:15 p.m. Vascular Rounds. Drs. Edward A. Edwards and Chilton Crane. D-Main, Peter Bent Brigham Hospital.
*12:30 p.m. Weekly Pathological Meeting. Joslin Auditorium, New England Deaconess Hospital.
*12:30–1:30 p.m. Weekly Staff Review of Autopsies. Dr. William A. Meissner. Joslin Auditorium, New England Deaconess Hospital.
*1:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*1:00 p.m. Massachusetts General Hospital Hand Clinic. The Clinics of the Massachusetts General Hospital.
*2:00 p.m. Rectal Clinic. Peter Bent Brigham Hospital.
*4:00–5:30 p.m. Fracture Lecture. Boston City Hospital.
*4:00–6:00 p.m. Overholt Thoracic Conference. Joslin Auditorium, New England Deaconess Hospital.
*6:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*7:30–9:30 p.m. Lahey Clinic Lecture. Joslin Auditorium, New England Deaconess Hospital.

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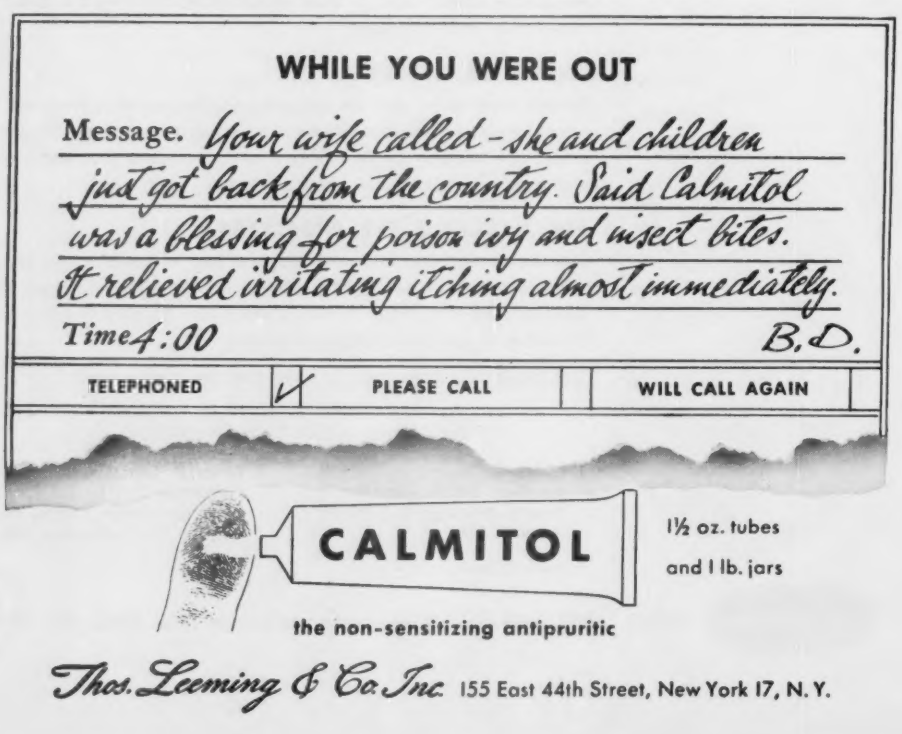
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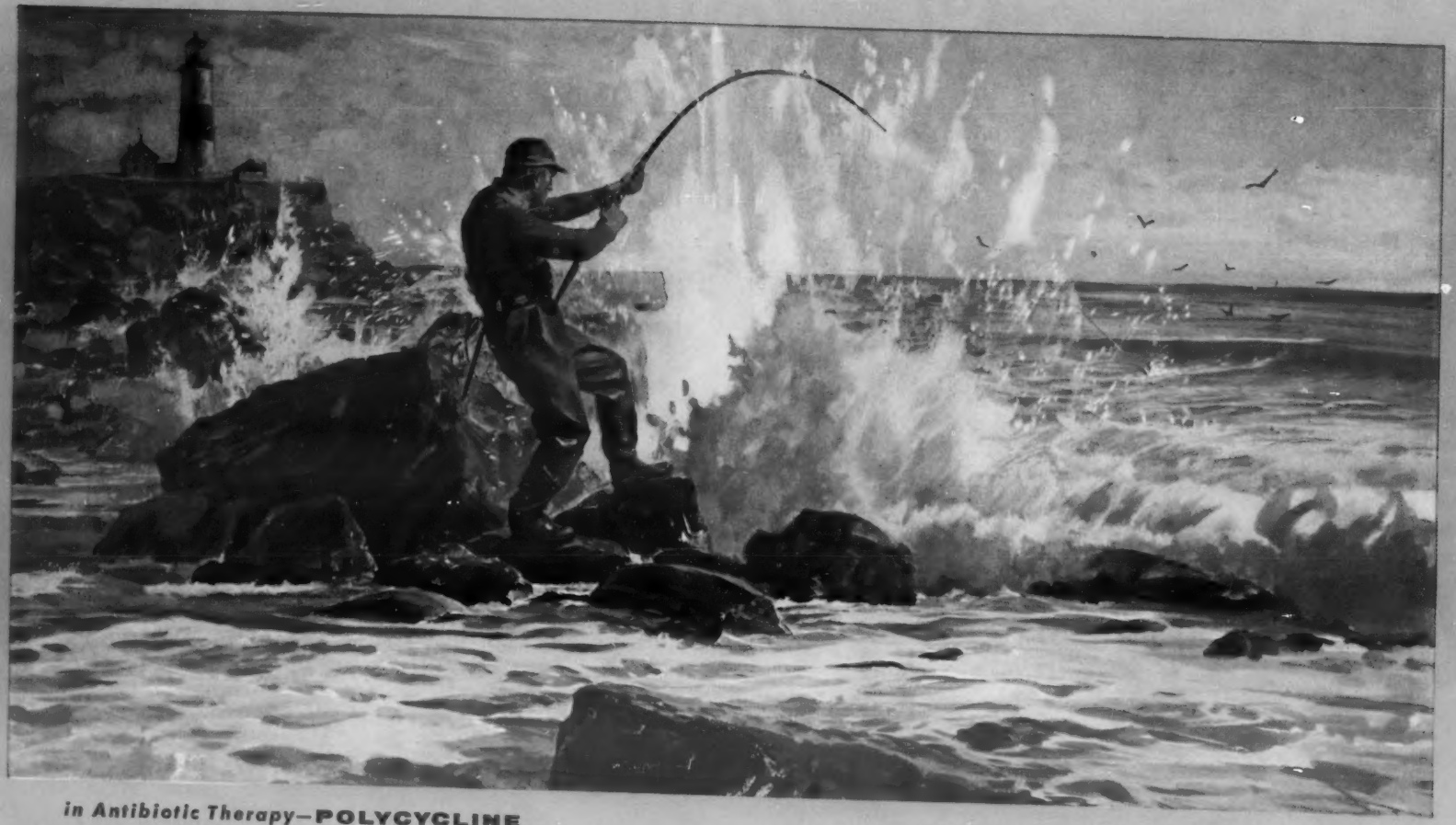

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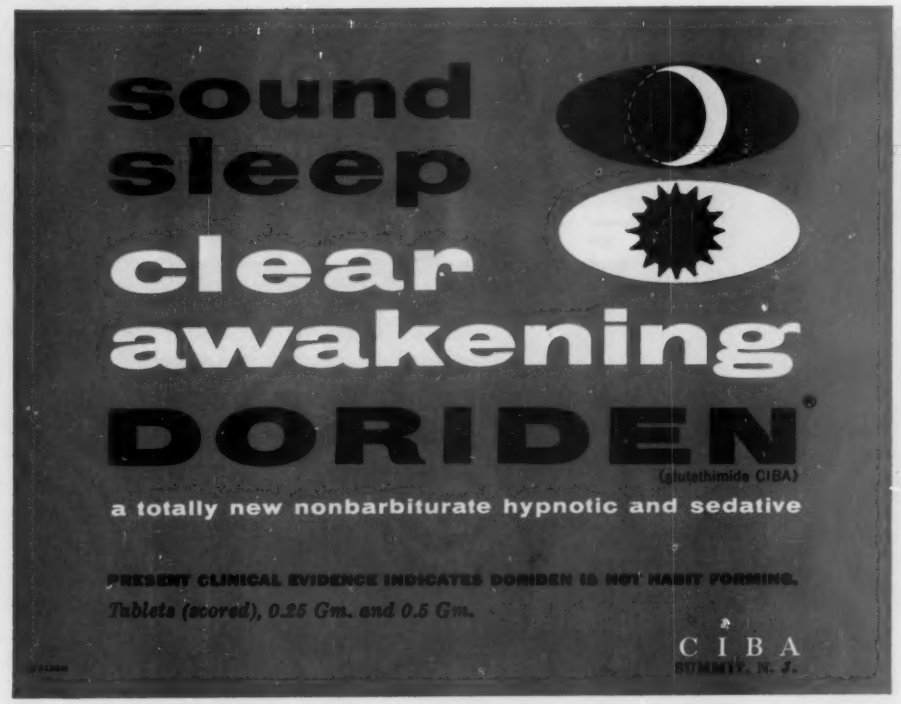

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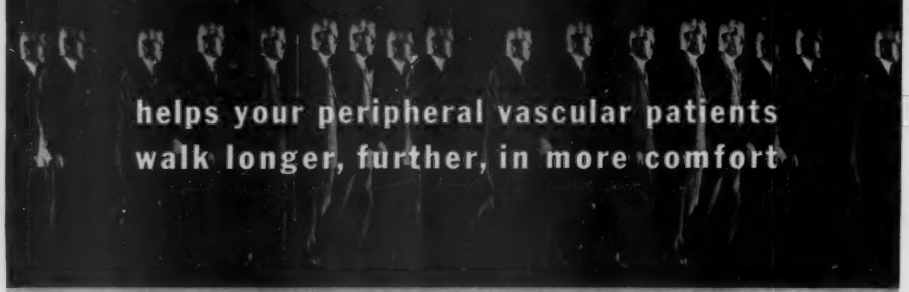

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1. Pomeranze, J. et al.: Angiology, June, 1955.
2. Freedman, L.: Angiology 6:52, Feb. 1955.

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Levin, S. J. Ped. Cl. of N. A. 1:975,1954.

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Naterman, H. L. The Journ. of Allergy. 24:60,1953.

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Unger, A. H. and Unger, L. Annals of Allergy. 10:128,1952.

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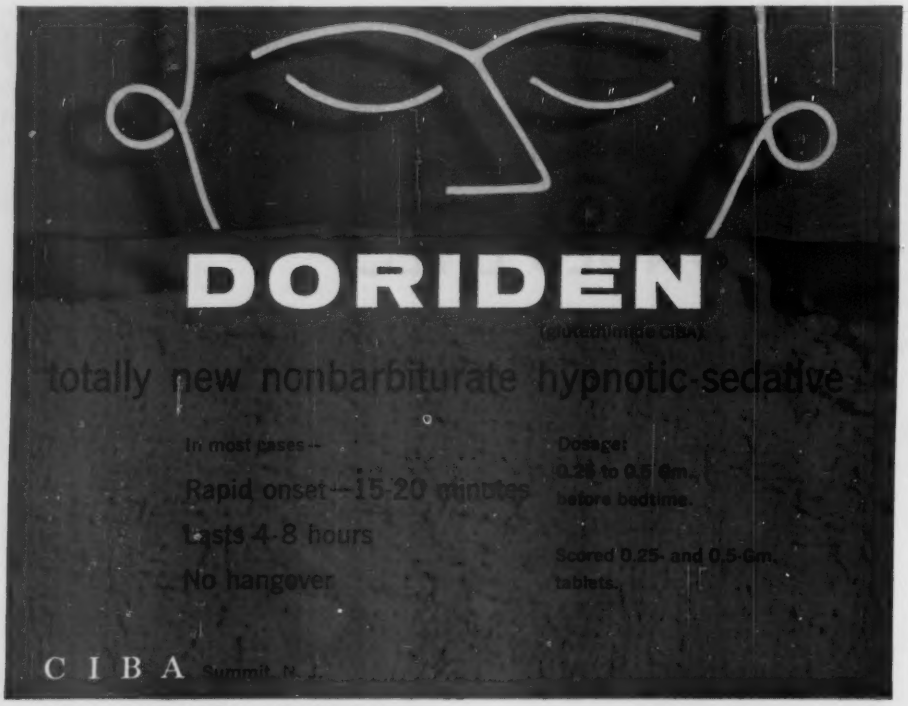

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(1) Jeans, P. C., in A. M. A. Handbook of Nutrition, ed. 2, Philadelphia, Blakiston, 1951, pp. 275-278.

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